VOLUME 78 • AUGUST 1958 • NUMBER 2

ARCHIVES OF DERMATOLOGY

Dermatology, Not Dermatologists
Nelson Paul Anderson

Effect of Ultraviolet Irradiation on the Spores of Trichophyton Sulfureum
Jacqueline Walker

Kwashiorkor
V. Medd Henington, Edward Caroe, Vincent Derbes, and Barrett Kennedy

The Central Fixation Phenomenon
Leon Goldman

The Problem of Syphilis Today
Herman Beerman

An Effective Simplified Serologic Test for Syphilis Employing Reiter Protein
George H. Kostant and Louise C. Kelcec

Larva Currens
Robert P. Arthur and Walter B. Shelley

Observations on the Role of Vehicles in Percutaneous Penetration
J. B. Shelmire Jr.

A Survey of Lupus Erythematosus in the University of Michigan Hospital Since 1948
Espey F. Cannon and Arthur C. Curtis

Treatment of Psoriasis with Folic Acid Antagonists
Walter F. Edmundson and William B. Guy

The British National Health Service and Dermatology
Patrick Hall-Smith

Giant Keratoacanthoma
Andrew Kallos

Asthma Melanodermica
L. J. A. Loewenthal and S. Shapiro

Pruritus and Proteolytic Enzymes
Samuel Monash and J. Frederick Woessner Jr.

The Mechanism of Solar Carcinogenesis
Bruce S. Mackie and Vincent J. McGovern

The Use of Amodiaquin (Camoquin) in the Treatment of Polymorphous Light Eruption
Milton M. Cahn, Edwin J. Levy and Bertram Shaffer

A Simple Portable Skin Microscope for Surface Microscopy
Leon Goldman

Eidamella Spinosa—Pathogenic for Man?
M. Paul Lazar and Helen MacLean

Granuloma Faciale
George F. Price

Oral-Perioral Leukokeratosis
Francesco Ronchese and Arthur B. Kern

Dermatitis of the Face Caused by Guanine in Pearly Nail Lacquer
Conrad Stritzler

The Human Ear Canal
Eldon T. Perry and Walter B. Shelley

Obituary: James R. Webster, M.D.

The New, Newer, and Newest

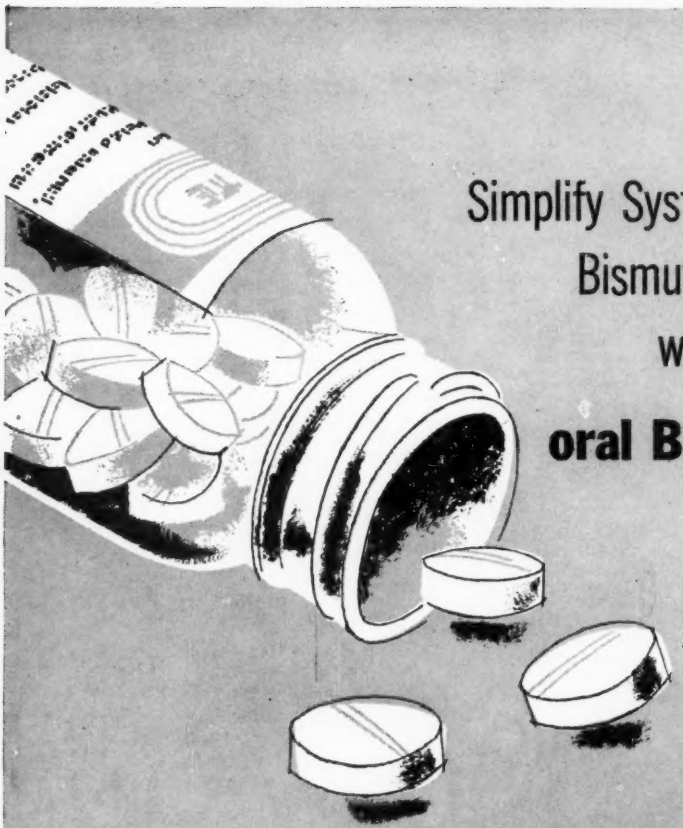
Chicago Dermatological Society

Cleveland Dermatological Society

Announcements

Books

AMERICAN MEDICAL ASSOCIATION PUBLICATION



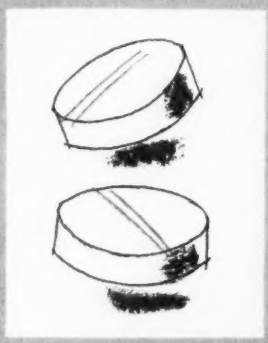
Simplify Systemic Bismuth Therapy with

oral BISTRIMATE®

(SMITH)

Whenever systemic bismuth therapy is indicated, prescribe BISTRIMATE (Smith). Its advantages are multiple.

- It is effective orally.
- It rapidly establishes and adequately maintains therapeutically active excretion levels of bismuth.
- It is well tolerated and permits ready control of bismuth levels.
- It is valuable in some cases of *lupus erythematosus, lichen planus* and *scleroderma.*[1]
- It is useful as adjunctive treatment in certain forms of *syphilis.*[1]



BISTRIMATE (Smith) is bismuth sodium triglycollamate. Each tablet is equivalent to 75 mg. of metallic bismuth.

1. New and Nonofficial Remedies, 1952.

For complete information about BISTRIMATE (Smith) write to:

CARROLL DUNHAM SMITH PHARMACAL COMPANY
New Brunswick, New Jersey
Established 1844

TABLE OF CONTENTS

VOLUME 78 AUGUST 1958 NUMBER 2

ORIGINAL ARTICLES

PAGE

Dermatology, Not Dermatologists
Nelson Paul Anderson, M.D., Los Angeles 145

Effect of Ultraviolet Irradiation on the Spores of Trichophyton Sulfureum
Jacqueline Walker, Ph.D., London 153

Kwashiorkor
V. Medd Henington, M.D.; Edward Caroe, M.D.; Vincent Derbes, M.D., and Barrett Kennedy, M.D., New Orleans 157

The Central Fixation Phenomenon
Leon Goldman, M.D., Cincinnati 171

The Problem of Syphilis Today
Herman Beerman, M.D., Philadelphia 174

An Effective Simplified Serologic Test for Syphilis Employing Reiter Protein
George H. Kostant, M.D., and Louise C. Kelcec, M.T., New York 181

Larva Currens
Robert P. Arthur, M.D., and Walter B. Shelley, M.D., Philadelphia 186

Observations on the Role of Vehicles in Percutaneous Penetration
J. B. Shelmire Jr., M.D., Dallas, Texas 191

A Survey of Lupus Erythematosus in the University of Michigan Hospital Since 1948
Espey F. Cannon, M.D., Redlands, Calif., and Arthur C. Curtis, M.D., Ann Arbor, Mich. 196

Treatment of Psoriasis with Folic Acid Antagonists
Walter F. Edmundson, M.D., and William B. Guy, M.D., Pittsburgh 200

The British National Health Service and Dermatology
Patrick Hall-Smith, M.D. (Edin.), M.R.C.P. (Lond. & Edin.), Hove, Sussex, England 204

Giant Keratoacanthoma
Andrew Kallos, M.D., New York 207

Asthma Melanodermica
L. J. A. Loewenthal, M.D., M.R.C.P., D.T.M. & H., and S. Shapiro, M.B., B.Ch., Johannesburg, Union of South Africa 210

Pruritus and Proteolytic Enzymes
Samuel Monash, M.D., and J. Frederick Woessner Jr., Ph.D., Miami, Fla. 214

The Mechanism of Solar Carcinogenesis
Bruce S. Mackie, M.B., B.S., D.D.M., and Vincent J. McGovern, M.D., Sydney, New South Wales, Australia 218

CLINICAL NOTES, NEW INSTRUMENTS AND TECHNIQUES

The Use of Amodiaquin (Camoquin) in the Treatment of Polymorphous Light Eruption
Milton M. Cahn, M.D.; Edwin J. Levy, M.D., and Bertram Shaffer, M.D., Philadelphia 245

A Simple Portable Skin Microscope for Surface Microscopy
Leon Goldman, M.D., Cincinnati 246

Eidamella Spinosa—Pathogenic for Man?
M. Paul Lazar, M.D., and Helen MacLean, M.S., Chicago 247

Granuloma Faciale
George F. Price, M.D., Brooklyn 248

Oral-Perioral Leukokeratosis
Francesco Ronchese, M.D., and Arthur B. Kern, M.D., Providence, R. I. 251

Dermatitis of the Face Caused by Guanine in Pearly Nail Lacquer
Conrad Stritzler, M.D., Jamaica, N. Y. 252

SCIENTIFIC EXHIBITS

The Human Ear Canal
Eldon T. Perry, M.D., D.Sc. (Med.), and Walter B. Shelley, M.D., Ph.D., Philadelphia 254

OBITUARIES

James R. Webster, M.D. 264

THE NEW, NEWER, AND NEWEST 267

SOCIETY TRANSACTIONS

Chicago Dermatological Society 268

Cleveland Dermatological Society 286

REGULAR DEPARTMENTS

Announcements 288

Books 288

A. M. A.
ARCHIVES OF DERMATOLOGY

VOLUME 78 AUGUST 1958 NUMBER 2

COPYRIGHT, 1958, BY THE AMERICAN MEDICAL ASSOCIATION

EDITORIAL BOARD

HERBERT RATTNER, Chief Editor
104 South Michigan Avenue, Chicago 3

HARVEY BLANK, Miami, Fla.
LOUIS BRUNSTING, Rochester, Minn.
J. LAMAR CALLAWAY, Durham, N. C.
A. C. CIPOLLARO, New York
GEORGE M. LEWIS, New York
H. E. MICHELSON, Minneapolis

AUSTIN SMITH, Editor, A. M. A. Scientific Publications
GILBERT S. COOPER, Managing Editor, Specialty Journals

SUBSCRIPTION RATES

Price per annum in advance, including postage: Domestic, $12.00. Canadian, $12.50. Foreign, $13.50. Price to students, interns, and residents, $7.00 in U. S. & possessions.

Single copies of this and previous calendar year, $1.25 each. Back issues older than two years are available through Walter J. Johnson, Inc., 111 Fifth Avenue, New York 3. Future reprints of back issues will be available through Johnson Reprint Corporation, 111 Fifth Avenue, New York 3.

Checks, money orders, and drafts should be made payable to the American Medical Association, 535 North Dearborn Street, Chicago 10.

AMERICAN MEDICAL ASSOCIATION Publication

Published monthly by the AMERICAN MEDICAL ASSOCIATION. Editorial and Circulation Offices: 535 North Dearborn Street, Chicago 10, Illinois. Publication Office: Thompson Lane, Box 539, Nashville 1, Tennessee. Change of Address: Notice to the circulation office should state whether or not change is permanent and should include the old address. Six weeks' notice is required to effect a change of address. Second-class mail privileges authorized at Nashville, Tenn., Aug. 6, 1956.

now you AEROSOLIZE

"Meti" steroid benefits directly on dermatoses

NEW METI-DERM® AEROSOL

"METI" STEROID TOPICAL

only spray touches skin... stops itching, edema, oozing

ease of application
smooth, even coverage
instant cooling relief
avoids rub-in irritation
no residue on skin
no messiness in hirsute areas
colorless, stainless, washable
greater economy

formula

Each spray can contains 50 mg. of prednisolone. A 3-second spray delivers approximately 0.5 mg., an amount sufficient to cover an area about the size of the hand.

packaging

METI-DERM Aerosol, 150 Gm. spray container.

METI-T.M.–BRAND OF CORTICOSTEROIDS BD-J 478

SCHERING CORPORATION · BLOOMFIELD, NEW JERSEY Schering

Instructions to Contributors

Articles, book reviews, and other materials for publication should be addressed to the Chief Editor. Articles are accepted for publication on condition that they are contributed solely to this journal.

An original typescript of an article, with one carbon copy, should be provided; it must be double or triple spaced on one side of a standard size page, with at least a 1-inch margin at each edge. Another carbon copy should be retained by the author.

The main title of an article may not contain more than eighty characters and spaces; a subtitle may be of any length.

The author's name should be accompanied by the highest earned academic or medical degree which he holds. If academic connections are given for one author of an article, such connections must be given for all other authors of the article who have such connections.

If it is necessary to publish a recognizable photograph of a person, the author should notify the publisher that permission to publish has been obtained from the subject himself if an adult, or from the parents or guardian if a child. An illustration that has been published in another publication should be accompanied by a statement that permission for reproduction has been obtained from the author and the original publisher.

Oversized original illustrations should be photographed and a print on glossy paper submitted. Prints of a bluish tinge should be avoided. Large photomicrograph prints will be reduced in scale unless portions to be cropped are indicated by the author. The author should submit duplicate prints of roentgenograms and photomicrographs with the essential parts that are to be emphasized circled, as a guide to the photoengraver.

Charts and drawings should be in black ink on hard, white paper. Lettering should be large enough, uniform, and sharp enough to permit necessary reduction. Glossy prints of x-rays are requested. Paper clips should not be used on prints, since their mark shows in reproduction, as does writing on the back of prints with hard lead pencil or stiff pen. Labels should be prepared and pasted to the back of each illustration showing its number, the author's name, and an abbreviated title of the article, and plainly indicating the top. Charts and illustrations must have descriptive legends, grouped on a separate sheet. Tables must have captions. ILLUSTRATIONS SHOULD BE UNMOUNTED.

References to the literature should be limited to those used by the author in preparation of the article. They should be typed on a special page at the end of the manuscript. The citation should include, in the order given, name of author, title of article (with subtitle), name of periodical, with volume, page, month—day of month if weekly or biweekly—and year. References to books must contain, in the order given, name of author, title of book, city of publication, name of publisher, and year of publication.

AMERICAN MEDICAL ASSOCIATION

535 North Dearborn Street **Chicago 10**

Higher and higher...
till the sky tipped over...
then down she came into the brambles
and sharp gravel and her dress was torn and there
were cuts and scratches...along with smudges of dirt

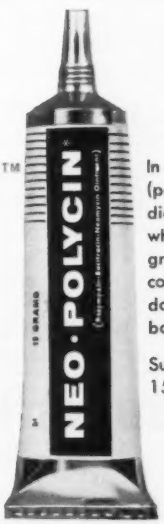
moral of the story: falling from a swing is bad even for a rag doll . . .
and when real children are hurt at play, topical infections often follow.

to prevent and control topical infections

prescribe **NEO-POLYCIN**™

...because it provides the 3 preferred topical antibiotics

Neomycin
Polymyxin
Bacitracin



In the unique Fuzene® (polyethylene glycol diester) base which releases greater antibiotic concentrations than do ordinary grease-base ointments.

Supplied in 15 Gm. tubes.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC., INDIANAPOLIS 6, INDIANA

The value of the instrument has been proven by its application for treatment of various skin disorders, such as camouflaging of vasacular nevi, undesirable stains, color matching of skin grafts with insoluable pigments, prutitus ani injections and infiltrations of skin with drugs and hormones.*

CONWAY DERMAJECTOR, MODEL B
ELECTRIC MACHINE FOR INTRADERMAL INJECTIONS
U. S. PATENTS No. 2,588,623, 2,840,076 and others pending.

*Ref.: Aaron, J. N. et al. "Vibra-Puncture Technique in the Treatment of Localized Neurodermatitis," Arch. of Dermat. May, 1958

FOR NEW TECHNIQUES IN THE TREATMENT OF NEURODERMATITIS

Some of the Important Features:

Conway Handpiece, small, light-weight and relatively noiseless, is held at 45 to 90 degree angle and manipulated like a writing pen.

The slotted tip is guided over the field of operation while the multiple needle injector projects into the skin with a uniform and positive penetration.

The desired depth of penetration can be instantaneously preset with instrument in motion; capable of delivering 10 to 60 strokes per second.

Patent-applied-for Self-Balancing Arm-Support neutralizes dragging and weight of the flexible cable, making the control of the handpiece effortless. The flexible cable is provided with a silencer and vibration absorber.

The motor is fully enclosed, operates on any current and needs no lubrication.

The entire instrument is chromium plated and all the parts can be readily sterilized.

ALSO AVAILABLE: CONWAY DERMAJECTOR, MODEL A, a portable unit with the same specifications as the Model B, but without stand. Multiple Needle Injectors in different width. Carrying case.

References:

Conway, H., and Docktor, J. P.: Neutralization of Color in Capillary Hemangiomas of the Face by Intradermal Injection (Tattooing) of Permanent Pigments, Surg. Gynec. & Obst. **85**:321, 1947.

Conway, H.: Evolution of Treatment of Capillary Hemangiomas of the Face with Further Observation on the Value of Camouflage by Permanent Pigment Injection (Tattooing), Surg., **23**:389, 1948.

Conway, H.: The Permanent Camouflage of Port-Wine Stains of the Face by Intradermal Injection of Insoluble Pigments (Tattooing), New York State J. Med., **48**:2040, 1948.

Conway, H.: Tattooing of Nevus Flammeus for Permanent Camouflage, J. A. M. A., **152**:866, 1953.

Conway, H.: "Tumors of the Skin," Charles Thomas, Springfield, Ill., 1956.

Hollander, E.: Treatment of Pruritus Ani by Tattoo with Mercury Sulphide, Arch. of Derm. & Syph., **38**:337, 1938.

Hailey, H., and Hailey, H.: Pruritus Ani et Vulvae, Arch. of Derm. & Syph., **40**:726, 1939.

Turell, R., Buda, A. M., and Martino, A. W. M.: Treatment of Pruritus Ani by Tattooing with Mercury Sulphide, Arch. of Derm. & Syph., **41**:521, 1940.

Turell, R.: Tattooing with Mercury Sulfide for the Treatment of Intractable Pruritus Vulvae and Ani, An Anatomical Study, Am. J. Obst. & Gynec., **42**:290, 1941.

For information, reprints and clinical demonstrations write to Robbins Instruments Company

ROBBINS ARE ORIGINATORS OF DERMABRASION EQUIPMENT

ROBBINS INSTRUMENTS COMPANY

Designers, Makers and Suppliers of Dermatological Specialties

CHATHAM, NEW JERSEY

CONTROL EMOTIONAL FLARE-UPS

that cause or aggravate **SKIN ERUPTIONS**

Miltown®

meprobamate (Wallace)

In neurodermatitis, atopic dermatitis, chronic urticaria, eczematoid dermatitis, lichen planus, psoriasis, pruritus ani, pruritus vulvae

Eighty per cent of 224 patients with a wide variety of skin disorders responded favorably to adjunctive therapy with Miltown.[2]

"is an effective addition to conventional dermatological therapy."[1]

- relieves anxiety and tension with exceptional safety
- suitable for prolonged administration
- does not impair physical efficiency or mental alertness

References: 1. Sokoloff, O. J.: Meprobamate (Miltown) as adjunct in treatment of anogenital pruritus. A.M.A. Arch. Dermat. **74**:393, Oct. 1956. 2. LeVan, P.: Clinical dermatologic studies of four chemically different tranquilizers. Clinical Med. **4**:1089, Sept. 1957.

Literature and samples on request

WALLACE LABORATORIES, *New Brunswick, N. J.*

CM-7260

FRIGIDERM®

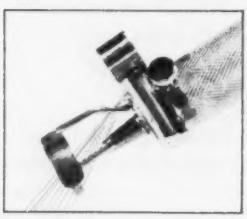
(100% dichloro-tetrafluoro-ethane...contains no ethyl-chloride)

SKIN REFRIGERANT–ANESTHETIC

*Widely Accepted for Local Anesthesia in Surgical Planing of the Skin**

JET-SPRAY PLANER

This hand-tooled, precision-built instrument with diamond fraises is available for most standard planing units. In ordering, please specify make of planing unit. Full information on request.



FRIGIDERM has been researched and developed to meet the expressed need of physicians for a well tolerated skin refrigerant-anesthetic...non-explosive, non-inflammable...having no general anesthetic properties.

Today, **FRIGIDERM** is one of the preferred products of its kind among Dermatologists everywhere.

FRIGIDERM quickly produces local anesthesia for surgical planing in the treatment of scarring due to acne, chickenpox, smallpox and trauma...multiple senile keratoses...fine wrinkling...traumatic tattoos.

Also for incision of furuncles, electrocautery to small cutaneous tags, flat warts, or for alleviation of needle pain during hypodermic injection.

This freezing agent can be delivered from the spray-top container shown above by easy finger pressure.

Now in the improved 8 oz. container — $2.00

Fully guaranteed for satisfactory performance
Available at your surgical supply dealer

*A.M.A. Archives of Dermatology, April 1955
Ref.: Wilson, J. W.; Luikari II, R.; Ayres III, S., Reprints available*

® REGISTERED TRADE MARK

BRACHVOGEL-HOVEY

1723 WEST SEVENTH STREET • DUNKIRK 4-9273 • LOS ANGELES 17, CALIFORNIA

unsurpassed

ANTI-INFLAMMATORY AND ANTI-ALLERGIC CORTICOSTEROID

WITH LOW DOSAGE
WITH NO SODIUM OR WATER RETENTION
WITH NO POTASSIUM LOSS
WITH LOW INCIDENCE OF OSTEOPOROSIS
WITH LOW INCIDENCE OF PEPTIC ULCER
WITH PSYCHIC EQUILIBRIUM RARELY DISTURBED

Supplied: 1 mg. scored tablets (yellow), bottles of 50 and 500;
2 mg. scored tablets (pink), bottles of 30, 100 and 500; 4 mg. scored tablets (white), bottles of 30, 100 and 500.

Aristocort®

Triamcinolone Lederle

Lederle LEDERLE LABORATORIES, A Division of AMERICAN CYANAMID COMPANY, Pearl River, N.Y.

NEW
TOPICAL
DIMENSIONS
in

Antiinflammatory
Antipruritic
Antiallergic
Bactericidal
Fungicidal
Protozoacidal
} action

INCORPORATED IN EXCLUSIVE ACID MANTLE® VEHICLE

pH 5.0

COR-TAR-QUIN™ Creme

ACID MANTLE® · hydrocortisone · stainless tar · diiodohydroxyquinoline

In subacute and chronic dermatoses, "especially where an inflammatory reaction was accompanied by increased scaling and lichenification with secondary infection such as is seen in seborrheic dermatitis, atopic dermatitis, contact dermatitis, and neurodermatitis."

—Rein, C. R., and Fleischmajer, R., Personal Communication.

also available COR-TAR-QUIN LOTION

Sig: Apply b. i. d.
½ oz., 1 oz., 2 oz., & 4 oz. tubes
either 0.5% or 1.0% hydrocortisone

DOME Chemicals Inc.
109 WEST 64 ST., NEW YORK 23, N.Y.
In Canada: 2765 Bates Rd., Montreal, P.Q.

in acute dermatoses

as well as subacute and chronic skin diseases

"prompt remissions"[1]

"...when the tar-steroid cream TARCORTIN was prescribed for patients presenting very acute episodes of atopic dermatitis, contact dermatitis, psoriasis, chronic infectious eczematoid dermatitis, and other eczematous dermatoses...we were able to achieve prompt remissions..."[1]

1. Welsh, A. L., and Ede, M.: J.A.M.A. 155:138, 1954.

Additional Clinical Publications on Tarcortin

Clyman, S. G.: Postgrad. Med. 21:309, 1957 • Bleiberg, J.: J. M. Soc. New Jersey 53:37, 1956 • Abrams, B. P., and Shaw, C.: Clin. Med. 3:839, 1956 • Welsh, A. L., and Ede, M.: Ohio State M. J. 50:837, 1954 • Bleiberg, J.: Am. Practitioner 8:1404, 1957

TARCORTIN®

Cream Hydrocortisone 0.5% and Special Coal Tar Extract 5% (TARBONIS®) in a greaseless, stainless vanishing cream base.

ALSO AVAILABLE: for dry, scaly eczemas, and when infection is present or anticipated

NEO-TARCORTIN®

Ointment Hydrocortisone 0.5%, Neomycin (as Sulphate) 0.35% and Special Coal Tar Extract 5%.

R&C REED & CARNRICK Jersey City 6, New Jersey

INDICATED:

NEO-MAGNACORT®

neomycin and hydrocortamate

TOPICAL OINTMENT

The first water-soluble dermatologic corticoid plus neomycin, for consistently outstanding control of contact dermatitis and other inflammatory dermatoses complicated by or threatened by infection.[1-6]

In 1/2-oz. and 1/6-oz. tubes, 0.5% neomycin sulfate and 0.5% hydrocortamate hydrochloride (hydrocortisone diethylaminoacetate hydrochloride) — MAGNACORT.

also available: MAGNACORT® Topical Ointment — in 1/2-oz. and 1/6-oz. tubes, 0.5% hydrocortamate hydrochloride (hydrocortisone diethylaminoacetate hydrochloride).

1. Howell, C. M. Jr.: Am. Pract. & Digest Treat. 8:1028, 1957. 2. Welsh, A. L.: Internat. Rec. Med. 169:775, 1956. 3. Robinson, H. M., Jr., et al.: Antibiotic Med. 3:461, 1956. 4. Frank, L.: A. M. A. Arch. Dermat. 75:876, 1957. 5. Janssens, J.: Le Scalpel 111:69, 1958. 6. Bereston, E. S.: Clinical Review 1:13, 1958

Pfizer

PFIZER LABORATORIES DIVISION, CHAS. PFIZER & CO., INC., BROOKLYN 6, NEW YORK

in acne therapy . . . 'Acnomel' conceals as it heals

Most acne patients want to hide their acne. Many use make-up that does hide acne lesions but does not help them. Flesh-tinted 'Acnomel', on the other hand, provides effective acne therapy that conceals as it heals.

Acnomel* Cream and Cake

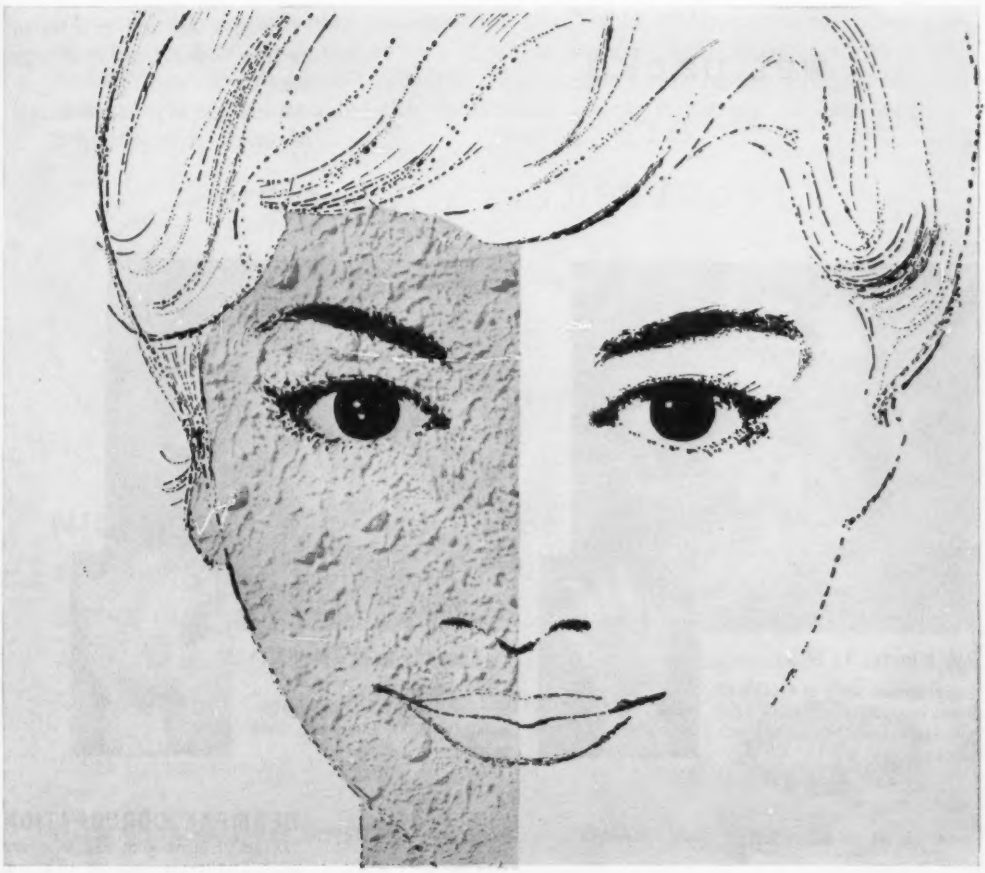
sulfur, resorcinol, hexachlorophene

'Acnomel' is simple to apply and to remove, and often brings definite improvement in a matter of days. Acnomel's special vehicle is free from oil, grease and wax, and holds active ingredients in prolonged, intimate contact with the skin.

Available: Cream for use at home; Cake for convenient use away from home.

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.



DERMPAK
Therapeutic Gloves

For a time-saving and convenient method of wet compress therapy dermatologists are turning to DERMPAK Therapeutic Gloves when treating eczematous processes of the hands.

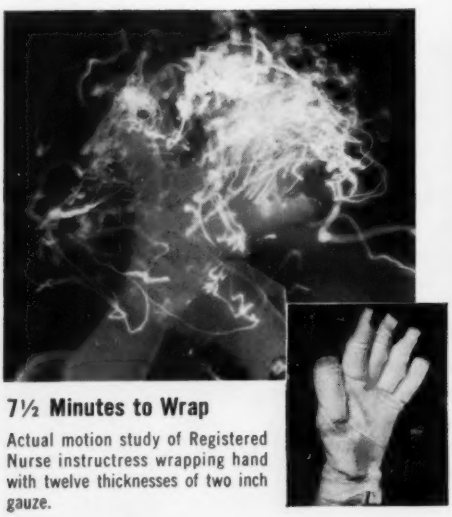
DERMPAK Gloves are widely accepted because they not only conserve valuable personnel time but meet with exceptional acceptance by the patient.

DERMPAK Gloves are made of 12-ply quilted hospital gauze . . . sterilized before packaging. They are durable and may be washed and re-used many times.

Available, one pair to a sealed package, in small, medium or large sizes.

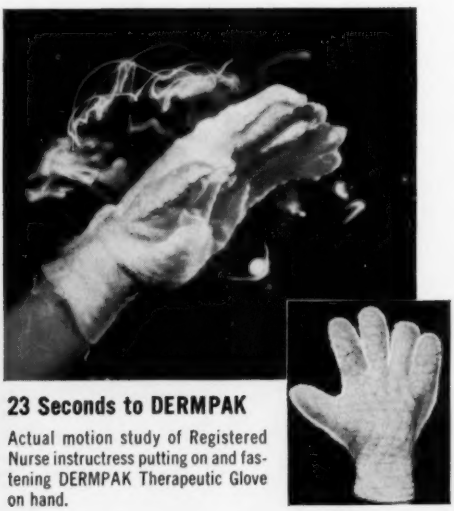
A free sample glove will be sent on request.

save
time
and
motion
where
wet packs
are
required...



7½ Minutes to Wrap

Actual motion study of Registered Nurse instructress wrapping hand with twelve thicknesses of two inch gauze.

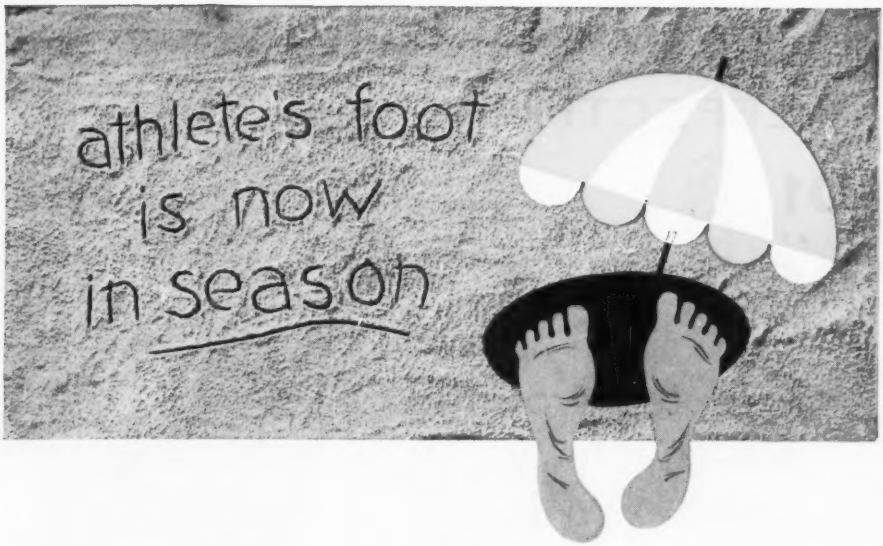


23 Seconds to DERMPAK

Actual motion study of Registered Nurse instructress putting on and fastening DERMPAK Therapeutic Glove on hand.

DERMPAK CORPORATION
282 East 5th Street • St. Paul, Minnesota

Manufactured and distributed under license from the Minnesota Dermatological Society.



Susceptibility factors play an important part in the occurrence and spread of athlete's foot. With the advent of warm weather, individuals who have had the disease are prone to exhibit recurrences or reinfection. Frequently, this can be prevented by the continuous prophylactic use of Desenex preparations.

Desenex®
OINTMENT — POWDER
SOLUTION

fast relief from itching

prompt antimycotic action

continuing prophylaxis

NIGHT and DAY treatment

AT NIGHT — Desenex Ointment (zincundecate) 1 oz. tubes. —

DURING THE DAY — Desenex Powder (zincundecate) — 1½ oz. container.

ALSO — Desenex Solution (undecylenic acid) — 2 fl. oz. bottles.

In otomycosis — Desenex Solution or Ointment.

Write for samples.

Maltbie

MALTBIE LABORATORIES DIVISION • WALLACE & TIERNAN, INC. • Belleville 9, N. J.

PD-75

new study confirms
EFFECTIVENESS

101
out of
106

infected wounds
successfully
treated with

Panafil®
OINTMENT

"...offers the surgeon another...efficient approach to the treatment of infected surface lesions."*

A recent clinical study* has shown PANAFIL Ointment to be effective in 101 out of 106 suppurative wounds and ulcerations involving a variety of bacterial organisms. PANAFIL, the only local medication used in these cases, "...produced uniformly successful results." Systemic antibiotics were employed only in the more severe infections.

Three ingredients in PANAFIL produce a continuous *cleansing-protecting-healing* action in the wound:

Papain—effective debriding enzyme, gently and safely removes debris and slough detrimental to the healing process.

Urea—augments the cleansing action of papain, especially in encrusted lesions.

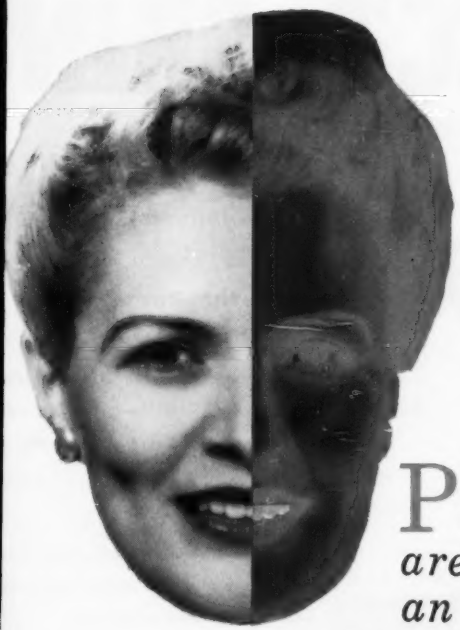
Chlorophyll derivatives—control inflammation, promote the growth of normal, healthy granulations.

PANAFIL Ointment contains papain 10%, urea U.S.P. 10%, and water-soluble chlorophyll derivatives 0.5% in a hydrophilic ointment base. Available in 1-ounce and 4-ounce tubes *on prescription only*.

*Miller, J. M.; Godfrey, G. C.; Ginsberg, M., and Papastrat, C. J., in Surgical Service, V. A. Hospital, Fort Howard, Maryland: Postgrad. Med. 22:609, 1957.

Rystan company • **Mount Vernon, N. Y.**

29459



PSORIATICS

are half personalities, for an uncomfortable person is only one half a personality

EPIDOL®

will help to restore the psoriatics' appearance and self-confidence.

EPIDOL is a clear, *adhesive, non-greasy,* rapidly drying, improved Wright Liquor Carbonis Detergens plus Salicylic Acid 3%.

EASY to apply. Applicator comes with every bottle.

EASY to remove. Readily washes off with soap and water.

Discover how rapidly and effective EPIDOL may relieve the discomfort and clear the lesions. It helps restore the patient's feeling of comfort. Your psoriatic patients may, once again, become confident, full personalities.

SUPPLIED: Bottles with applicators: 3 fl. oz.—6 fl. oz.

Samples, literature and reprints are available. Just write to:

Spirt & Co., Inc.
WATERBURY, CONN.

TO PROTECT SKIN

AGAINST A WIDE RANGE OF IRRITANTS

- *in industry*
- *in the home*

Silicote provides an important advance in protectin skin from dry and aqueous irritants—prophylacticall to prevent skin maceration, and therapeutically t exclude water, soap, and other substances from derma toses that may be aggravated by them.

Clinical tests show that Silicote provide excellent protection against soap an water and soluble cutting oils.[1]

The protective property of Silicote purely mechanical. Protective efficienc is necessarily determined by the natur and frequency of exposure. Frequency c application should be adjusted to pro vide adequate protection with minimum dosage.

SUGGESTED DOSAGE: Cleanse area thoroughly wit soap and water. Apply thin film as required and ru in well. If skin is exposed constantly to irritant, appl every 2-4 hours, or as needed to provide protectior It is not necessary to remove original coat befor applying subsequent coats. Any objectionable greasi ness may be removed by wiping with a dry cloth, o washing gently with soap and water.

CONTRAINDICATIONS: Do not use on weeping o infected areas.

In Housewife's Eczema
Industrial Dermatoses
Chapping—Chafing
Intertrigo
Diaper Rash
Chronic Dermatoses
Aggravated by Soap
and Water

SILICOTE CONTAINS
30% dimethicone (silicone) in a specially prepared petrolatum base. Contains no water-soluble ingredients.

Send for samples and literature

1. Shaw, J. M., and Crowe, F. W.: Skin Protective Ointments. Arch. Dermat. & Syph. 71: 379, 1955.

SILICOTE
SILICONE OINTMENT

ARNAR-STONE LABORATORIES, INC. **MT. PROSPECT, ILLINOIS**

In Canada: Brent Laboratories, Ltd., Toronto

NOW... an advanced ACTH

SIGNIFICANTLY IMPROVED

CORTROPHIN®-ZINC

(Corticotropin-Alpha Zinc Hydroxide)

A unique electrolytic process* of manufacture gives a fine, easily resuspended aqueous suspension of Cortrophin-Zinc with these therapeutic advantages:

★ **VIRTUALLY PAINLESS** . . . . Unsurpassed patient acceptance.

★ **HIGH PURITY** . . . . . Virtually pure ACTH with fewer mg. of foreign protein per injection.

★ **RAPID ACTION** . . . . . New form stimulates peak adrenal output within two hours.

★ **LONG ACTION** . . . . . Provides ACTH activity for several days.

★ **ECONOMICAL** . . . . . Lower total ACTH dosage and fewer injections required.

Cortrophin-Zinc is indicated in the treatment of more than 100 diseases, including rheumatoid arthritis, bronchial asthma, allergies and hypersensitivities, bursitis, serum sickness, conjunctivitis and other eye diseases, ulcerative colitis, atopic dermatitis and other skin diseases.

★ **ASK YOUR ORGANON REPRESENTATIVE OR WRITE FOR CLINICAL AND EXPERIMENTAL REPORTS SUBSTANTIATING THESE CLAIMS.**

SUPPLIED: 5-cc vials containing 40 and 20 U.S.P. units of corticotropin per cc; 1-cc ampuls containing 40 and 20 U.S.P. units of corticotropin, with sterile disposable syringes.

Pat. Pending
Available in other countries as Cortrophine-Z.

Organon inc. ORANGE, N. J.

A new highly effective

SHALE TAR

Metashal®

Solubilized Colorado Shale Tar, Stiefel

"especially impressive...in atopic dermatitis of all ages and stages"[4]

Compatible with all standard dermatologic drugs, such as hydrocortisone, salicylic acid, menthol and iodochlorhydroxyquin.

METASHAL, a Colorado shale tar that is different from conventional coal tars, has been found to be "especially impressive . . . in atopic dermatitis of all ages and stages."[4] Another investigator has reported that it "seems to be particularly effective in many cases of atopic dermatitis" in infants and children.[1]

Confirming previous studies,[2] a report of 414 cases of atopic and contact dermatitis and other skin diseases showed that shale tar therapy resulted in a favorable response in 96.3%.[3]

In another report of 365 cases from several different investigators, "excellent" or "very good" results were obtained with METASHAL in 93.75% of atopic dermatitis cases in infants and children, and fair to excellent results in 94.4% of atopic dermatitis cases in juveniles and adults.[4]

SUPPLY: METASHAL OINTMENT, containing 8.7% shale tar, for heavier, lichenified, subacute and chronic lesions. METASHAL LOTION, containing 18% shale tar in zinc oxide-talc shake lotion, for moist, more acute phases. Available only on your prescription.

SEND FOR SAMPLES.

REFERENCES: 1. Howell, C. M.: N. Carolina M.J. 18:322, 1957. 2. Brandt, R., and Dexter, H.: J. Invest. Dermat. 15:163, 1950. 3. Brandt, R., and Dexter, H.: Ibid. 19:409, 1952. 4. Brandt, R., and Szolomejer, W.: A.M.A. Arch. Dermat. 76:241, 1957.

STIEFEL®

FOUNDED 1847

STIEFEL LABORATORIES, INC. • Oak Hill, New York •

Canadian Representatives: Winley-Morris Co., Ltd. Montreal 29, Que.

SOAP

AGGRAVATES...

PROLONGS

DERMATITIC CONDITIONS

Soap, because of its high alkalinity, can be a primary cause of skin irritation. Or it can aggravate a dermatitic condition already present...make it worse...and even prolong it. Lowila is soap free...does not contain alkali, fatty acids or perfumes. Lowila cleanses tender or dermatitic skin without irritation...maintains the normal acid mantle of the skin...creates an environment favorable to therapy and normal healing.

Lowila should replace your patients' regular bar soap for washing, bathing and shampooing. It easily works into a rich, gentle lather in both hard and soft water.

Soap irritation wastes sound dermatologic therapy . . . recommend Lowila Cake.

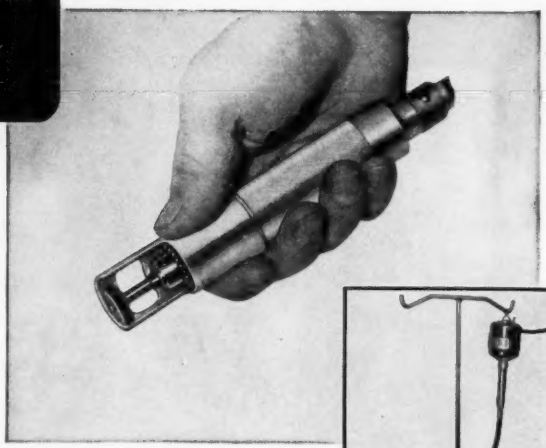
WESTWOOD *PHARMACEUTICALS* *WRITE FOR SAMPLES*

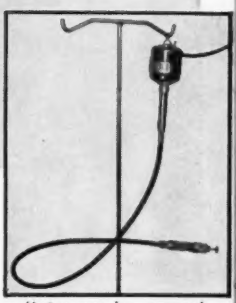
Division of Foster-Milburn Company, 468 Dewitt Street, Buffalo 13, New York

use **LOWILA®**
CAKE
to cleanse without irritation

The Stryker

WIRE BRUSH UNIT for SKIN PLANING





Motor can be suspended at a suitable height to be free of "drag" on the flexible cable.

6 Valuable Features of the STRYKER WIRE BRUSH UNIT

- GUARD REDUCES BLOOD SPLASH—yet permits clear view of planing area.
- HANDPIECE CANNOT BE DAMAGED by accidentally catching the brush in gauze, gloves, or hair.
- 22,000 RPM'S AT FULL SPEED—for most effective abrasion, yet lower speeds are available.
- HANDPIECE IS HAND-CRAFTED OF ALUMINUM—with stainless steel bearings for cool operation and long life. Can be cold sterilized or autoclaved.
- SENSITIVE, VARIABLE SPEED footswitch control.
- STAINLESS STEEL JACOBS CHUCK—firmly holds any brush, or abrasive wheel.

PRICES

Stryker Wire Brush Unit $219.00

Consists of: Motor and cable, handpiece, variable footswitch and carrying case (foam rubber lined.)

Less carrying case $205.00

Wire Brushes—Order Separately.

Standard Small Wire Brushes (2mm. rounded cutting side) ¾" diameter in soft, regular, or coarse abrasion, each $6.00

Optional Equipment

No. 1310 Standard Mayo Table, Chrome plated, 40 lb. base, holds accessories and provides mount for motor above 5 ft. $110.00

ORTHOPEDIC FRAME COMPANY
420 ALCOTT AVENUE
KALAMAZOO, MICHIGAN

☐ Send me the Wire Brush Unit on approval.
☐ Send me Brochure.

NAME_____

ADDRESS_____

CITY_____ STATE_____

Orthopedic **ORTHOPEDIC FRAME CO.**
Kalamazoo Michigan

Distributed in Canada by: Fisher & Burpo, Ltd., Winnipeg
Exclusive Agent for Export: Schueler & Co., 75 Cliff St., N. Y.

A.M.A. ARCHIVES OF
DERMATOLOGY

Dermatology, Not Dermatologists

NELSON PAUL ANDERSON, M.D.,† Los Angeles

Election to the presidency of an organization such as this bestows high honor upon the recipient, but at the same time it endows him with the privilege as well as imposes upon him the duty of imparting to its membership his ideas and ideals, insofar as they are pertinent to its welfare and to the specialty in general. Some of the following points probably merit debate, but I believe them all to be worthy of your thought and consideration.

Public Relations

Dermatologic public relations, in the principal phase, consists in the everyday manner in which every dermatologist and his nurses, secretaries, technicians, and other personnel meet and handle their patients. It includes the way in which they are greeted and conducted to and from diagnostic and treatment rooms and the finesse and skill with which the examinations, consultations, diagnoses, and treatments are performed. Every move must be carried out consistently with courtesy, kindness, tact, and efficiency. It is not enough to admit that these are the best principles of good medical practice toward which to strive; they must be always the basic ones. They can be accomplished only through the constant effort of each individual dermatologist in his own practice. However, such accomplishment may be aided by example in practice and in preceptor training, by round-table discussions, and by lectures such as those given last year at our Academy meeting by Dr. Lovshin and this year by Dr. Roth. As Lord Lister once said: "The true physician may cure rarely, alleviate frequently but comfort always."

Another and extremely important phase of public relations consists in education for the public concerning dermatology. This is a field in which the dermatologist must seek the advice, help, and assistance of experts. Never for one moment should we underestimate the power of the printed word. Somehow or other it is magically clothed with authority and in many ways is superior to either the spoken word or words accompanying pictures such as photographs, movies, or television. There is a very definite place for articles, pamphlets, booklets, or news items intended for use by the lay public. The same holds true for radio or television talks, broadcasts, or lectures.

We would be well advised, I believe, to give serious consideration to the furtherance of some sort of highly organized educational program among the laity, on

† The original handwritten, roughly drawn manuscript for this paper was found on Dr. Anderson's desk after his sudden death on Dec. 1, 1957. It was apparent that he had intended to read it a few days later to the Board of Directors of the American Academy of Dermatology, as one of his Presidential duties. After it was presented and read to the Board, the Members unanimously agreed that it merited publication. Dr. J. Walter Wilson edited the paper slightly and managed to retain Dr. Anderson's style.

a year-round continuous basis. Dermatologists are not on the same level as "beauty specialists." They are physicians who have received education bearing on this subject in college, in medical school, and in residence training programs. All but a few are certified by the American Board of Dermatology, Inc. The great majority belong to the American Academy of Dermatology and Syphilology. Material prepared for publicity by dermatologists would inevitably be much closer to the truth than the usual "beauty advice"; I believe that in addition it could be made equally dramatic and interesting. Certainly our specialty has as much, and probably more, to offer in interesting the layman as any other group. If you doubt this, consider the amounts spent yearly in this country for cosmetic and beauty preparations.

The encouragement of articles in lay publications and of the productions of material for motion pictures and television should be a function of either our Committee on Public Relations or our Educational Committee. Attention should also be given to publicity and education within the profession itself, in such publications as *Scope Weekly*, *M.D.*, and other similar quasiprofessional newspapers or magazines, as well as in pharmaceutical trade journals.

The annual meetings of not only our Academy but other national or regional dermatological organizations offer great opportunities to tell the public about dermatology and its accomplishments. Fortunately, the Academy has had such a program in operation for the past few years, developed almost entirely through the efforts of our Secretary, Dr. James R. Webster. The furnishing of copies of lectures to be delivered, copies of the program to be presented, and descriptions of the scientific exhibits is of great value and should be utilized whenever possible. In general, the cooperation of our members in this matter has been good, but it could be even better.

Already other professional groups, particularly radiologists,[1] ophthalmologists, pathologists,[2] and internists have seen fit to sponsor and use their great influence and resources in the furtherance of such a program of public relations as that outlined above. I believe that dermatologists should follow their example and use this extremely potent force to a greater degree than heretofore to further our own broad specialty.

Geriatrics

There is increasing need and demand for dermatologic participation in the care of chronic illness in old people. There are now some 14,000,000 people 65 years of age and over in our country. The cutaneous problems of this group merit additional consideration by dermatologists. This is another field in which federal, state, county, and city governmental agencies are moving in and taking over, partially, at least, because of the comparative vacuum which exists.

Rehabilitation

Dermatologists have given little attention to the rehabilitation of persons suffering from active cutaneous disorders or their sequelae. Our English colleagues, notably MacKenna and Heller, have been active with regard to this problem, but there have been only a few American contributions. One of these has been made recently by Levy and Barnes, working in cooperation with the Leg Amputee Clinic at the University of California. Their scientific exhibit at our 1957 meeting carried several messages: (1) the exact problem confronting one type of handicapped person; (2) the value of cooperation of dermatology with other medical groups; (3) the implications that such types of work possess wider ramifications than one would see after only a cursory examination.

All sorts of funds, especially federal and state, are available in this field of vocational rehabilitation. Certainly the painter who is sensitive to turpentine, the construc-

tion worker who is allergic to cement, and the lithographer and others who are sensitive to chromates require rehabilitation just as much as the crippled child, the amputee, or any other physically disabled person. I recommend that all of you give some serious thought and study to this much-neglected facet of dermatology. If we are not prepared to offer advice and constructive suggestions, the allocated funds will either go to others by default or, perhaps worse, be administered in our own field by those not entirely competent.

The American Medical Association has a committee on rehabilitation. Certainly, dermatology has as much right to be represented on this committee as has any other branch of medicine.

Improvement of the Status of Dermatology

Dermatology continues to suffer encroachment from all of the specialties, and nowhere is this truer than in medical education. That portion of the public which is well informed does not need to be "sold" on dermatology. The practicing physician, regardless of whether he is a general practitioner or specialist, values and appreciates dermatologic help. Nevertheless, in some of the medical schools of the nation dermatology is neglected and treated as a stepchild or even worse. There are many reasons for this, and the blame probably rests equally on the dermatologist and nondermatologist. We need not go into the reasons for the lack of stature of dermatology in medical education, for this is not the place to discuss them. Nevertheless, since the sole function of our Academy is education, it appears that this organization should do what it can to improve this situation at every level.

For years I have believed that lack of appreciation of the many contributions of dermatology to medicine was due in great part to a deficient knowledge of its scope. It would seem advisable that every month the dean of each medical school should receive gratis a copy of the A. M. A. Archives of Dermatology and the *Journal of Investigative Dermatology*. Also, perhaps from time to time a personal letter could be sent calling attention to some article of particular interest in the current issue, especially if one appeared which impinged on internal medicine or on teaching. Perhaps also a request could be included to see that the copy eventually found its way to the department of dermatology, there to be kept and used in the clinic and to become a part of the departmental library. The execution of such a plan would undoubtedly require the cooperation of other dermatologic societies—more particularly the American Dermatological Association and the Society for Investigative Dermatology.

I would also like it if the dean of every medical school in the Mississippi Valley were to receive a personal invitation to attend any of our Academy meetings. Often such men could also be utilized on the program, as has been done on occasion in the past. Other specialty groups have not neglected those in positions of power and influence.[3]

Selection of Dermatologic Trainees

Another aspect dealing with the advancement of dermatology has to do with the encouragement, selection, and development of "embryo" dermatologists. I am sure that many of us realize that a not inconsiderable number of the products of our present system of training are far from being ideal representatives of our specialty. In some respects this is our own fault and constitutes a cross which we must carry. Nevertheless, all of us are products of our times and as such are influenced, molded, and shaped by the thoughts, by the philosophy, and by the actions of those who are in positions of influence, power, and responsibility. This is especially true for those charged with the responsibility of teaching this subject.

Why, for example, does any medical student completing his four years of medical school and starting his year or two of internship decide on dermatology as a specialty? The psychiatrists have looked at us and given their viewpoint. Menninger says that "Dermatology, like psychiatry, deals to a large extent with perverse expressions of emotional disorders" . . . "the dermatologist relies chiefly upon his eyes." Menninger suggests that dermatologists have a special "appreciation of the graphic arts." [4] In comparing dermatology with psychiatry, a field in which he is an expert, he points out that the patients of a dermatologist are often "under a cloud" in that the "public suspects them of being untouchable and loathsome and guilty of exaggerating their suffering." "Dermatologists are accused of making meaningless Latin diagnoses and applying placebo ointments to inconsequently ill patients."

"The most frequent reason given by the dermatologist for entering the specialty is 'the challenge behind the obvious'. . . . Dermatological diseases are puzzling, obscure, often difficult to diagnose and still more difficult to treat. The ostentatious pride with which some doctors announce their ignorance of dermatology seems to stimulate others to attempt to fathom the mystery." Occasionally, one chooses this field because the patients usually do not die. "Quite a number mentioned the influence of an enthusiastic teacher or the desire to exploit a good visual mind." Menninger sums it all up by saying: "But all that this really adds up to is that even the conscious reasons for electing dermatology are as unknown as the etiology of some dermatological lesions."

It is probable that many of us were motivated by different ideas, hopes, and desires than those expressed by Menninger. Some were stimulated by the example set by teachers in medical school or by attending men in the hospital where they served their internship; others wished to obtain relief from the terrific burden faced by the physician in general practice. Some have turned to a specialized field because of a belief that it is probably better to know a good deal about one subject rather than a little about a lot of subjects. In another smaller group, increasing as our specialty grows older, we find the sons of dermatologists following in their fathers' footsteps.

In only one field—obstetrics and gynecology—has anyone attempted to evaluate statistically the caliber of men choosing a particular specialty. Gardner [5] investigated all graduates from Northwestern University Medical School during the 10 years between 1934 and 1943. This study was initiated by the American Gynecological Society and represents the report of one member of a committee of three. At Northwestern, at least, the figures caused him to conclude that obstetrics and gynecology has not attracted its proportionate share of "talented" recent graduates. Gardner realized that "talented" is a term "extremely difficult to define and equally hazardous to assess." Nevertheless, this was attempted by use of the class scholastic standing of the students, because it "is actually the only practical and readily available yardstick for classifying recent graduates in respect to their potentialities for future professional achievements." One tangible "future achievement" was deemed to be specialty board certification. This latter criterion seemed to be valid because data were presented to show that such certification has been achieved most frequently by those (Northwestern) graduates with the highest class standing. Several figures of Gardner's article are worth noting: 636, or 40%, of the graduates are certified. In the first 10% of the graduating class 64% (99) were certified; 56% (289) in the first third, 42.5% (219) in the middle third, and only 23% (118) in the lowest third of these classes were certified.

To be able to draw conclusive comparisons, Gardner of necessity had to tabulate

all of the specialties. His figures for dermatology show that there were 13 certified specialists (2.1%). None of these were in the first 10% of their classes; five were in the first third, six, in the middle third, and two, in the last third of their classes. What should be a "normal" proportionate share of "talented" recent graduates for a specialty? According to Gardner, it should be 16% of those ranked in the first 10%, and 46% of those certified should be from the upper third of their classes. With only 13 recent graduates certified in dermatology and syphilology, no significant conclusions can be drawn. Nonetheless, it seems fairly certain from Gardner's analysis that some specialties are attracting more than their proportionate share from the group of "better than average" students. Actually, the fields of medicine and surgery have been dominant. Gardner states that "such monopoly of the better prospects has been calamitous not only for obstetrics and gynecology, but also for orthopedic surgery, ophthalmology, radiology, urology, pediatrics, otolaryngology and dermatology-syphilology. Actually all of these latter specialties attract 50% less than their proportionate share of the first 10% of these classes, or 20% less than their share of those students in the upper third of their classes."

In other fields as well this problem of the type of young person entering a certain specialty has been reviewed, studied, and approached by concerted action. Recently the American Foundation for Allergic Diseases has granted $500 to each of 20 junior medical students for spending the summer between their junior and senior years in becoming acquainted with research and training in this field. These particular awards were made possible by a grant to the foundation by the Gustavus and Louise Pfeiffer Research Foundation.[6] This same American Foundation for Allergic Diseases also offers two fellowships in research and clinical allergy, one at the University of Pennsylvania and the other at Washington University. These fellowships are for two years each and are for those who have completed one or two years in study of internal medicine. The stipend for the first year is $4500.00 and for the second year is $4750.00, and it includes laboratory and travel expenses of $750.00 for the two-year period. This makes a total of $10,000.00 per fellowship for a two-year period.

Lest we mistakenly believe that the allergists are the only ones attempting to entice the talented undergraduate medical students, let me cite that according to Dr. Paul R. Hawley, Director of the American College of Surgeons, it was arranged that medical students from 36 medical colleges could attend as guests the 43d annual Clinical Congress of the College, "the world's largest meeting of surgeons," held this year in Atlantic City, N. J., Oct. 14-18, 1957. This student participation program was initiated last year as an educational contribution by the College, by action of the Board of Regents. Students were selected by vote of their classmates, and medical colleges sending representatives to the Congresses are to be rotated. This year, schools to be represented were from Chicago, eastern United States, Canada, and Puerto Rico.

It would seem that consideration should be given similarly by dermatologists in general and perhaps by the Academy in particular to the possibility of attendance at our meetings of undergraduate medical students who have shown special interest in our field.

One of our younger and dedicated dermatologists is awarding $100.00 annually as a prize to the undergraduate student in his school who submits the best essay on a dermatologic subject. This has succeeded in interesting a considerable group of medical students in dermatology and has resulted in securing several excellent students who have already entered into graduate training in this field.

In the graduate field considerable stimulus has been provided by the annual contests held by the American Dermatological Association. Some local dermatological societies, notably the Detroit Dermatological Society, also present annual awards to papers of merit.

Fellowships in Dermatology

The Osborne Fellowship in Pathology, established in 1951 for work to be done by dermatologists for one year at the Armed Forces Institute of Pathology, has now been awarded six times, to these recipients: Victor C. Hackney, M.D., of Indianapolis; David William Kersting, M.D., of Milwaukee; Tobias Roger Funt, M.D., of Fort Lauderdale, Fla.; Brian Snell Potter, M.D., of St. John's Hospital, London; James H. Graham, M.D., of Washington, D. C., and Paul Hirsch, M.D., of Washington, D. C. Dr. Graham, the Osborne Fellow last year, is staying on another year on the basis of a research grant from the National Institutes of Health. This will enable him to work on the study of Bowen's disease which was begun last year.

Only a few other fellowships in dermatology are known to me. These are the Gillette-Toni Fellowship in Dermatology at Northwestern[1] and Research and Teaching Fellowships in Dermatology at the New York Skin and Cancer Unit of New York University-Bellevue Medical Center.[8,9] There are undoubtedly others. Certainly one of the oldest was the James Nevins Hyde Fellowship, at Rush Medical College. What has become of this, I do not know. Only recently an annual award of $1000 for research on psoriasis was announced.[10] It is amply evident that the fellowships available in dermatology are too few, particularly when contrasted with the long-standing fellowships in endocrinology endowed by Schering Corporation, The Upjohn Company, Ayerst Laboratories, and E. R. Squibb & Sons (see any issue of *The Journal of Clinical Endocrinology and Metabolism*) or with the 12 fellowships sponsored by the American Academy of Pediatrics.[11]

Sources of Funds for Dermatologic Advancement

There is probably no specialty in the healing arts which has received less public support than dermatology. At the present time there are over 80 charitable organizations which solicit funds from a very generous public for health purposes. There are 15 organizations devoting their services to the blind (ophthalmology); 2 organizations for the hard of hearing (otology); 12 groups (if we include muscular dystrophy and poliomyelitis) striving to help the handicapped (orthopedics); 5 groups for mental health, including epilepsy and alcoholism (psychiatry); 5 groups helping neurologic disorders, including cerebral palsy, epilepsy, multiple sclerosis, and paraplegia. In internal medicine[12] there are foundations dealing with the heart, diabetes, nephrosis, arthritis, hemophilia, tuberculosis, and fibrocystic disease. There are at least six organizations attacking the cancer problem. Hay fever and the common cold, leprosy, and social diseases have their organizations. Some of these associations do even better than to extend from the "cradle to the grave" or from "womb to tomb," starting with planned parenthood and following through infancy, childhood, adolescence, adult life, and old age. However, there is no similar organization dealing exclusively with cutaneous disorders, although a few may be said to touch briefly on this subject. These latter include the cancer groups, leprosy and tuberculosis organizations, and perhaps those for venereal diseases. When one considers that these 80 or more groups derive annual funds in excess of $4,000,000,000 from some 30,000,000 American citizens, one can realize that "In the old days charity was a virtue; today it is an industry." One such group in this country has made grants of over $20,000,000 since 1948.

It would seem that considerable thought should be given to tapping the sources of such unparalleled generosity so that some funds are made available for dermatologic purposes.

There is no doubt that the cosmetic industry should be one of the chief sources of funds for dermatologic purposes, for many reasons. As Lehman, of the Food and Drug Administration, says in an editorial discussing the cosmetic problem: "The need for increasing the scope and number of investigations relating to the fundamental problem of skin physiology, biochemistry, pharmacology and toxicology cannot be stressed too strongly."

Another potential source, one perhaps more immediately available, is the drug industry. The situation at present is somewhat as follows: Relatively small funds and grants are available from drug manufacturers but usually only for certain express purposes, principally the extolling of a certain drug for either internal or external use and the proof that such a preparation is to be preferred above all others. The financial assistance in such cases is frequently minimal and more often is nothing more than furnishing the amount of the drug used in the investigation. Frequently, such studies end in the publishing of unscientific results praising unjustifiably the virtues of the preparation used. Controls are frequently absent or, if attempted, are often faulty. The pharmaceutical company finally obtains a publication in a scientific journal from which reprints are circularized to the medical profession, thus becoming nothing more than advertisements. The author has another publication to add to his list of publications, another "scalp for his belt," so to speak. Undoubtedly the pharmaceutical company is pleased, but the physician has become nothing more than a Madison Avenue huckster or in some instances has virtually replaced the traveling patent medicine man of days gone by.

In spite of the desires of the schools of pharmacy to the contrary, at least 90% of all local preparations for use in cutaneous disorders are made up in their final form by drug houses and dispensed by drug stores merely by removing or changing a label. There are many reasons for this, and it presents advantages as well as disadvantages, which need not be discussed here. The point is that this is an extremely profitable activity of the pharmaceutical industry, because of which it would seem reasonable to expect at least the more enlightened companies to furnish some funds for unrestricted research in dermatology. One leading pharmaceutical house has recently established 50 scholarships for postgraduate medical training. It is to be hoped, perhaps with undue optimism, that a certain number of these scholarships will be granted to dermatologists.

Another source of funds, some of which should be available for dermatologic purposes, are those controlled by industry and by labor. The huge field of industrial dermatoses represents a large segment of the whole of dermatology. The pathogenesis, the prevention, and the treatment of dermatologic conditions of industrial or occupational origin are problems which are and should be in all propriety attacked by industry, labor, and insurance carriers, but every such effort should include cooperation with dermatologists. Recently the sum of $100,000 was set aside by a typographers union to study the particular problem of chromate dermatitis in that industry. If a solution were found it would be of great value to the cement, pottery, automotive, and other industries as well.

In connection with funds, I should like to call your attention to a little-known book or directory entitled "American Foundations and Their Fields," now in its seventh edition,[13] which lists some 4100 foundations and trusts. The group which publishes this also publishes a periodical entitled "American Foundation News," which represents current authoritative information in the foundation field.

Establishment of a Dermatologic Foundation

I am sure that I am not the first to recognize a very definite need—yes, indeed, almost a necessity—for the establishment of some type of foundation which could serve as a central point for the collection of funds earmarked for dermatologic purposes. Undoubtedly there would be many pitfalls, headaches, and heartaches in such an undertaking, such as problems of tax exemption, fund raising, personnel, lay participation, disbursement of funds, and many, many others. The Society of Investigative Dermatology, Inc., had a Committee to Study Sources of Funds and Possible Uses of Funds. Apparently, the committee's report was not acted upon, and the committee disbanded.[14] Much the same fate met the proposal of the Psoriasis Research Association. The more recent, somewhat similar organization, the Psoriasis Research Foundation, has so far not been strikingly successful.

In the meantime new foundations are being formed all the time. One of special interest to dermatologists is the National Lupus Erythematosus Foundation, Inc. Other groups seem to be able to go ahead with the formation, establishment, and development of what might be termed narrow of single-purpose foundations. Whether this is good or bad I do not choose to discuss. Others[15] have questioned the modern trend toward the "Disease-a-Month Club." At any rate, this problem is here, and one accomplishes nothing by ignoring it.

The fact remains that at present there is not a single dermatologic institution having tax-exemption privileges which is in the position to solicit and receive funds of any nature.

Conclusion

I trust that none of the foregoing will be misconstrued. Any criticisms which are present are meant to be constructive. I believe that the satisfactory solution to any problem is found only after the realization that it exists and only after it is openly brought to the attention of those concerned. This I have attempted to do. Let no one think that I am so naïve as to believe that I know all the answers.

Every dermatologist possesses his share of the natural human desire to help advance himself in his stature in his community. I firmly believe that he can best accomplish this by directing his efforts less inwardly and selfishly toward his own problems and more outwardly toward the improvement of dermatology in general and at all levels. Dermatology should be the first consideration, not the dermatologists.

REFERENCES

1. Scott, W. G.: Public Relations and Educational Programs of the American College of Radiology, Editorial, Am. J. Roentgenol. 78:728, 1957.

2. Konzelmann, F. W.: Public Information Program As It Applies to Scientific Papers Published in the Journal or Presented at the Annual Meeting, Am. J. Clin. Path. 26:933, 1956.

3. Furstenberg, A. C.: The Viewpoint of a Dean, Tr. Am. Acad. Ophth. 61:515, 1957.

4. Menninger, K.: Psychological Factors in the Choice of Medicine as a Profession, Bull. Menninger Clin. 21:99, 1957.

5. Gardner, G. H.: Too Many Talented Prospects By-Pass Obstretrics and Gynecology, Am. J. Obst. & Gynec. 70:582, 1955.

6. Allergy Foundation Awards, Medical News, J. A. M. A. 164:2065, 1957.

7. Fellowships, News, Quart. Bull. Northwestern Univ. M. School 31:187, 1957.

8. Announcement, J. Invest. Dermat. 27:271, 1956.

9. Dermatological Fellowships, Medical News, J. A. M. A. 163:1371, 1957.

10. Research in Psoriasis, Medical News, J. A. M. A. 164:2063, 1957.

11. News and Notes, J. Pediat. 51:615, 1957.

12. Announcements, Dis. Chest. 32:xvii (Aug.) 1957.

13. Rich, W. S.: American Foundations and Their Fields, Ed. 7, New York, American Foundations Information Service, 1955.

14. The Society for Investigative Dermatology, Inc., J. Invest. Dermat. 27:204, 1956.

15. Zuelzer, W. W.: Presidential Address: Society for Pediatric Research, A. M. A. Am. J. Dis. Child. 93:1, 1957.

Effect of Ultraviolet Irradiation on the Spores of Trichophyton Sulfureum

JACQUELINE WALKER, Ph.D., London

Morphologic variation in culture is not uncommon with some species of dermatophytes. It has been the basis of many reported new species, the names of which have subsequently passed into synonymy. Emmons [1] observed spontaneous variation in an old, single-spore culture of Microsporum gypseum growing on horn, and he was able to isolate from the strain six distinct and stable variants.

Smith [2] showed that variation in fungi could be induced by ultraviolet irradiation. Emmons and Hollaender,[3] working with Trichophyton mentagrophytes and wavelengths of 2280 A. to 2950 A., showed that both mutant production and lethal effect were greatest in the region of wavelengths 2537 A. and 2650 A. They believed that these variants, because of their character and permanence, represented true genetical changes and could, therefore, be regarded as mutants.

Later Hollaender and Emmons [4] showed that mutants in fungi could be produced by irradiation with bright sunlight on a clear day in June, in the Northern Hemisphere, and they obtained a mutation rate of up to 6% with Aspergillus terreus spores.

During the past three years, specimens from 102 cases of tinea capitis caused by the Trichophyton tonsurans group of fungi were cultured in this laboratory. Approximately 90% of the cultures isolated were of the typical yellow Trichophyton sulfureum type; others were of the white, tan, or pale rose color described by Georg [5] in her study of the group. However, a few isolates, suspected of belonging to this group because of the contacts of their human source, could not be identified with certainty by their morphology in culture. In order to obtain some idea of the range of variation to be expected in this species group, a freshly isolated strain of T. sulfureum was subjected to ultraviolet irradiation.

Submitted for publication Jan. 2, 1958.

Mycological Reference Laboratory, Public Health Laboratory Service, London School of Hygiene and Tropical Medicine.

Materials and Methods

A recently isolated, richly sporing, typical deep sulfur-yellow strain of T. sulfureum was selected from the routine diagnostic specimens, and a single spore isolate was made from it by using the modification of the Sass spray method suggested by Skinner, Emmons, and Tsuchiya.[6] This new strain was grown on malt extract agar for six days at 26 C, and spores collected from the surface of the culture were suspended in sterile isotonic saline solution and filtered through sterile cotton wool to remove, as far as possible, any fragments of mycelium. The resulting filtrate had a spore density of approximately 125,000 per milliliter. A 3 ml. volume of the suspension was placed in a sterile exposure cell and rapidly and constantly agitated throughout the experiment. After withdrawal of 0.1 ml. for the control, the remainder of the suspension was exposed to a wavelength of 2537 A. for periods varying from 60 to 320 seconds *; after each exposure 0.1 ml. was withdrawn. The 0.1 ml. volumes were diluted 1:50 with sterile isotonic saline solution, and ten 0.1 ml. quantities of each were plated onto malt extract agar plates. This represented a random sampling of the spores which had been exposed. The plates were incubated at 26 C; the control plates were counted after seven days and the irradiated plates after 14 days, as one of the effects of irradiation was to retard the growth even in those spores which later gave

* The source of ultraviolet light consisted of a Hanovia UV lamp, 12 in., 15 watt model fitted with a Type 1 filter. Exposures were made at a distance of 7.0 in. from the tube.

TABLE 1.—*Lethal Effect and Variant Production Resulting from Exposure of T. Sulfureum Spores to 2537 A.*

Length of Exposure, Sec.	Total No. of Colonies on 10 Plates *	Total No. of Variants on 10 Plates *	Variants, %
Control	2,500	0	0
60	2,397	0	0
120	472	56	11.9
150	261	39	14.9
180	145	23	15.9
210	82	19	23.2
240	36	9	25.0
320	5	1	20.0

* These platings were made from a 1:49 dilution of the suspension of spores used for irradiation.

morphologically normal colonies. The control plates were checked again after 14 days.

Results

Although the experiment was repeated three times, no mutant appeared on any of the 30 control plates sown with nonirradiated spores. By comparison with the control plates an initial retardation of growth was evident in all the irradiated spores both mutant and nonmutant. However, this retardation was not shown by the next subculture. The percentage of mutants among the surviving irradiated spores rose to a peak at 240 seconds and then dropped rapidly, but the total number of spores surviving exposures of 320 seconds and longer was very small. There did not appear to be any relation between the length of exposure and the type of mutant induced. Table 1 gives the figures for one of the three experiments; the results of the other two were very similar.

According to their pigmentation and gross morphology the mutant colonies could be grouped roughly into five categories. But, as was found by Emmons and Hollaender [7] with T. mentagrophytes and by Newcombe [8] with Streptomyces sp. T. 12, some variation in minor properties was represented in each category.

Apart from the stable mutants a number of unstable variants appeared on the primary plates. These were induced at all exposure times and reverted to morphologically normal colonies on subculture. Emmons pointed out that this early reversion might be due to the colonies arising from two or more of the irradiated spores lying in very close proximity, in which case the nonmutant spore, although initially retarded by irradiation, would grow normally on subculture and mask the variant. The mutants have now been maintained in culture for 18 months, during which time they have been subcultured 12 times. Evidence of instability in culture was shown in a number of strains by colonial sectoring. As indicated in Table 2, this phenomenon was irrespective of the duration of the original spore irradiation. Two forms of sector were recognized: a full sector which extended from the center of the colony to the margin and suggested very early instability, and a shallow sector which extended inward to only about one-half the radius of the colony and indicated a change at a later stage of colony growth. In the majority of instances this sectoring represented an apparent reversion to the normal type of T. sulfureum as judged by macroscopic and microscopic examinations, but platings made from the sector usually showed about 90% of the colonies of the normal type and 10% of the variant form. Subcultures made from the variant portion of the original colony were generally of the variant type only, but after one or two transplants some of them showed sectoring. Nevertheless, many of the original variant strains have shown no tendency toward sectoring or reversion, and these are now regarded as stable mutants.

The mutants have been maintained on four media: (1) 4% malt-extract agar; (2) 1% glucose+1% Bacto-peptone agar; (3) 4% glucose+1% Oxoid-peptone agar; (4) 3% Allen and Hanbury Eu-

TABLE 2.—*Sectors Developing in Subcultures of Variant Colonies Two to Twelve Months After Irradiation*

Length of Exposure, Sec.	Original No. of Variants	No. Showing Full Sector	No. Showing Shallow Sector
120	56	3	12
150	39	2	4
180	23	1	4
210	19	0	2
240	9	0	2
320	1	0	0

Fig. 1.—Initial single-spore isolate of Trichophyton sulfureum on malt-extract agar.

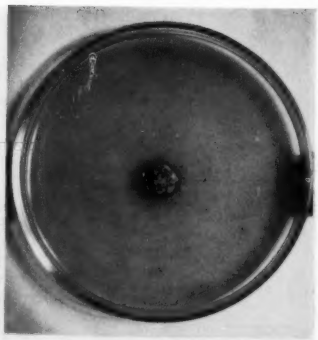


Fig. 2.—Purplish-brown cerebriform mutant on malt-extract agar.

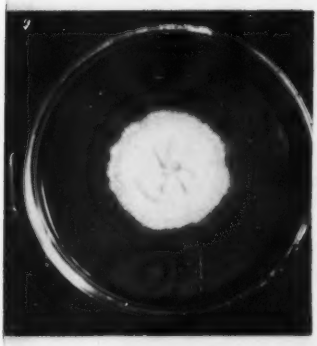


Fig. 3.—White mutant on malt-extract agar.

Fig. 4.—Faviform mutant on malt-extract agar.

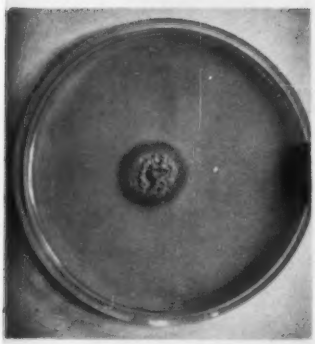


Fig. 5.—Yellow glabrous mutant on malt-extract agar.

Fig. 6.—Mutant of the red group showing white powdery surface and a diffusible red pigment, on malt-extract agar.

Fig. 7.—Mutant of the red group with purplish, almost glabrous colony on malt-extract agar.

Fig. 8.—An instable variant colony producing a sector of apparently normal growth.

peptone agar. The initial single spore isolate of T. sulfureum (Fig. 1) produced on these four media a sulfur-yellow crateriform colony with a powdery surface, a serrated margin, and brownish pigmentation on the reverse. Microscopic examination of the growth on all four media showed the presence of many microconidia and some macroconidia.

Of the stable mutants the largest number (29%) came into the purplish-brown cerebriform mutant category and were induced at 120-, 150-, 180-, 210-, and 240-second exposures. The growth was rather restricted (10 mm. in four weeks at 26 C) on the malt, 1% glucose and peptone media, but in a few cases, less so on the 4% glucose.

The colonies were heaped up and cerebriform with serrated margins and a powdery surface. All the colonies were of a purplish-brown color on the malt and glucose media, but a few were a deep-tan color on the 3% peptone agar; little or no diffusible pigment was produced. Microscopically all the colonies had a similar morphology. Normal baton-shaped microconidia were present in the powdery surface. In many cases the conidiophores appeared to be foreshortened and the conidia, although in thyrsi, gave the structures a bottle-brush appearance. As the colonies aged, large numbers of chlamydospores appeared.

The white mutant form, which accounted for 22% of the mutants, was induced at 120-, 150-, 180-, 210-, and 240-second exposures. The growths were not restricted and produced white velvety or powdery colonies, crateriform, cerebriform, or acuminate in shape; the margins were sometimes serrated and sometimes entire; the reverse of the colony was light brown.

Microscopically, all the colonies showed normal rather baton-shaped microconidia in thyrsi and a few produced macroconidia. The characters remained constant on all four media tested, and the colonies came within the limits of species designated T. tonsurans (T. crateriforme), T. sabouraudi (T. acuminatum) and T. cerebriforme.

Nineteen per cent of the mutants produced glabrous-heaped cerebriform colonies varying from light buff to light brown in color on all media. They were induced at 150-, 180-, 210-, 240-, and 320-second exposures. In gross morphology many were indistinguishable from Trichophyton schoenleini. The microscopical morphology was that of a "faviform type" of colony, namely, numerous chlamydospores, and broad and distorted hyphae, and many hyphae with forked tips. Representatives of the types of morphology seen in T. concentricum, T. violaceum (T. glabrum), and T. verrucosum could be found. However, the characteristic chandeliers and knuckle-bone hyphae of T. schoenleini were never seen.

Colonies belonging to the yellow glabrous mutant group accounted for 7% of the stable mutants and were induced at 120-, 150-, 210-, and 240-second exposures. The colonies on all media were glabrous, irregularly folded, with serrated margins, and bright yellow to orange in color, and they could easily be confused with the common orange type of Microsporum ferrugineum described by Ota.[9]

The microscopical examination of all the colonies showed only chlamydospores and hyphal swellings.

There was greater variation in gross morphology among the members of the red mutant group than in the preceding categories. They were induced at 120-, 150-, 180-, 210-, and 240-second exposures and accounted for 23% of the mutants.

On malt-extract agar they produced colonies varying in color from pale pink to dark red. Some had powdery surfaces and produced a red pigment which diffused slightly into the medium resembling closely the powdery forms of T. rubrum. Others formed dark purplish-red flat almost glaborus colonies and no diffusable pigment. However, on the glucose and peptone media they all produced pink or tan powdery

colonies, some of which were folded and others flat, but no diffusible pigment was seen.

In the microscopic examination, the colonies with a powdery surface showed numerous typical microconidia in thyrsi; the semi-glabrous colonies showed chlamydospores and only a few microconidia.

Conclusion

By ultraviolet irradiation of a suspension of spores from a young culture of T. sulfureum, it was possible to induce a heritable variation in cultures developing from a proportion of the irradiated spores. These variants were of two kinds—one showed an inherent tendency toward dissociation with partial reversion to the parent type; the other, with stable characters, represented a true mutation. These stable mutants were divisible into five groups, four of which bore a more or less close resemblance to other dermatophyte species. These four were designated (*a*) the white mutant, which resembled T. tonsurans, T. sabouraudi, or T. cerebriforme; (*b*) the faviform mutant resembling T. schoenleini in gross morphology and T. violaceum (T. glabrum), T. verrucosum, and T. concentricum microscopically; (*c*) the yellow glabrous mutant which closely resembled Microsporum ferrugineum, Ota; (*d*) the red mutant, some strains of which resembled T. rubrum. The fifth group, the purplish-brown cerebriform mutant, although presenting the characters of the dermatophytes, did not resemble any known species.

It is noteworthy, however, that even with a lethal irradiation of 320 seconds which reduced the proportion of viable spores to 1 in 500, only about 20% of the cultures developing from the survivors showed variation from the parent type; the remaining 80%, except for an initial retardation of growth which did not occur in subsequent transplants, were apparently normal. No explanation of this resistance was reached.

Summary

The spores from an original single-spore isolate of Trichophyton sulfureum were subjected to ultraviolet irradiation of a wavelength of 2537 A. Five categories of mutants were induced which differed from the parent strain in colony morphology and color. No mutants were found in the unirradiated controls. Some of the induced mutants resembled other dermatophytes.

London School of Hygiene and Tropical Medicine, Keppel St. (W. C. 1).

REFERENCES

1. Emmons, C. W.: Pleomorphism and Variation in the Dermatophytes, Arch. Dermat. & Syph. 25:987, 1932.

2. Smith, E. C.: The Effects of Radiation on Fungi, in Biological Effects of Radiation, New York, McGraw-Hill Book Company, 1936; cited by Emmons and Hollaender.[8]

3. Emmons, C. W., and Hollaender, A.: The Action of Ultraviolet Radiation on Dermatophytes: II. Mutations Induced in Cultures of Dermatophytes by Exposure of Spores to Monochromatic Ultraviolet Radiation, Am. J. Bot. 26:467, 1939.

4. Hollaender, A., and Emmons, C. W.: Induced Mutations and Speciation in Fungi, Cold Spring Harbor Sym. Quant. Biol. 11:78, 1946.

5. Georg, L. K.: Studies on Trichophyton Tonsurans: II. Morphology and Laboratory Identification, Mycologia 48:354, 1956.

6. Henrici, A. T.: Henrici's Molds, Yeasts, and Actinomycetes: A Handbook for Students of Bacteriology, Ed. 2, edited by C. E. Skinner, C. W. Emmons, and H. M. Tsuchiya, New York, John Wiley & Sons, Inc., 1947, p. 60.

7. Emmons, C. W., and Hollaender, A.: Relation of Ultraviolet-Induced Mutations to Speciation in Dermatophytes, Arch. Dermat. and Syph. 52:257, 1945.

8. Newcombe, H. B.: Radiation-Induced Instabilities in Streptomyces, J. Gen. Microbiol. 9:30, 1953.

9. Ota, M.: Sur 2 Espèces nouvelles de dermatophytes en Mandchourie Microsporum ferrugineum et Trichophyton pedis, Bull. Soc. path. exot. 15:588, 1922.

Kwashiorkor

Report of Four Cases from Louisiana

V. MEDD HENINGTON, M.D.; EDWARD CAROE, M.D.; VINCENT DERBES, M.D., and BARRETT KENNEDY, M.D., New Orleans

The chief credit for the description of the disease known as kwashiorkor belongs to Dr. Cicely D. Williams.[1] * Like many other diseases, it had been described earlier, first, it would appear, by Czerny and Keller, in 1906 in Germany. They observed the condition, which they called *Mehlnährschaden*, in young children and ascribed it to excessive carbohydrate in the diet. A number of other descriptions followed, notably by Proctor, in 1927, who described a condition in young children manifested by slimy diarrhea, swelling of the feet, and a curious black desquamation of the skin; by Lieurade, in 1932, who observed it in West Africa, and by a number of other observers whose descriptions, however, are not always sufficiently detailed to permit one to say that the condition in question was or was not kwashiorkor. The comprehensive review of the literature by Trowell, Davies, and Dean[2] contains a number of references to early articles of this kind, particularly to two in which, it might seem, kwashiorkor was reported in the United States. Careful examination of these two publications suggests that there is no warrant for this assumption.

According to Williams,[1] whose definitive article was published in 1953, only Czerny and Keller, Proctor, and Lieurade preceded her in the field, although none of their publications had made their way to the Gold Coast when she described what she had reason to believe was a new disease entity. She added that the connection between kwashiorkor and the disease described by Czerny and Keller in Germany in 1906 was fully established by Waterlow in 1948.

Williams' first report on kwashiorkor was based on the observation of five children, four of whom died, in the south, or so-called colony, part of the Gold Coast. This report appeared in 1933 and was followed two years later by a second, more extended report.

In her first report, Williams called the disease a nutritional disease of childhood associated with a maize diet. In her second report she used the term kwashiorkor, a "cumbersome word," she noted, which was merely a confession of ignorance. Although the disease has continued to be known as kwashiorkor, the origin of the term is still a matter of dispute. It was given to the disease by the Accra people, to whom the condition was well known, and it is a temptation to assume that it refers to the change in the color of the hair which is one of its manifestations. In Williams' opinion, the term refers to the raw areas in which the skin peels off in severe and acute cases. Kwashi, she also pointed out, is the name for a boy born on a Sunday but is used generically, as one would use the term Johnny or Tommy. Another theory is that the word means displaced from the breast and refers to the custom of Gold Coast mothers, who, although malnourished themselves, and with very little milk, breast-feed

Received for publication July 7, 1957.

Read at the 77th Annual Meeting of the American Dermatological Association, Inc., Belleair, Fla., April 12, 1957.

From the Departments of Dermatology, Louisana State University School of Medicine and Tulane University of Louisiana School of Medicine, and the Independent Service, Charity Hospital of Louisiana at New Orleans.

* Unless otherwise indicated, all citations of other authorities are from this comprehensive article.

their young until the next child is born, generally at the end of two years.

At any rate, whatever its derivation and origin, the nomenclature, as Williams observed, makes no unwarranted assumptions with respect to etiology or pathologic process and has, as a *Lancet* editorial noted, the merit of neutrality.

Kwashiorkor has been reported from every part of Africa and from China, India, Malaya, Indonesia, Fiji, and the Philippines. It has also been reported from Hungary and Italy, from the Caribbean Islands, and from various parts of Central and South America. To our knowledge, it has not yet been reported in the United States.

For this reason, we are reporting the following four cases, which are apparently the first to be reported in this country. The condition, if untreated, produces permanent undesirable sequelae, while if adequate treatment is instituted in time the manifestations are completely reversible. The disease, furthermore, can be suspected, if not diagnosed absolutely, almost on first glance if the history of the case is known. No doubt there are other patients in the United States suffering from it (our fourth case was observed while this paper was in preparation), and it is important that they be recognized and treated.

Cases 1 and 4 are presented as fairly typical instances of kwashiorkor as seen outside of Africa, where, the reports indicate, the disease is severest. The second and third patients, sisters of the first, probably represent the mild, or forme fruste, manifestation of the disease, to use Goldman's[3] description. The fourth patient represents the typical "displaced" child.

Case Histories

CASE 1.—An 11-year-old Negro girl was brought into Charity Hospital of Louisiana at New Orleans, Jan. 14, 1933, by her parents. For the preceding two weeks she had been acutely ill with vomiting and diarrhea and had also complained of headache. Two days before admission she had been given a vermifuge, which had increased the diarrhea, and she had been passing worms by rectum ever since. For the past month she had had occasional cramping abdominal pains, accompanied by swelling and bloating, and it was for this reason that the father had given her (and the other children in the family) a vermifuge. Over about this same period of time her legs had been swollen and she had been in a state of what the father described as "sleepiness."

The girl had been born in Charity Hospital, after seven months of gestation. For a time after discharge she had received an evaporated milk (Pet Milk) formula, from which, apparently at a very early age, she went straight to a diet of red beans and rice. She had never had either orange juice or a vitamin supplement. She was 1 of 14 living children. The mother, 46 at this time, had hypertension and was deaf and almost blind. She had had 19 pregnancies in all; 3 children had been stillborn, and 2 others had died in infancy.

Physical Examination.—The patient was obviously underdeveloped. She was 44.8 in. tall and weighed 39 lb. This put her, in spite of her age of 11 years, within the lower 2 percentiles for 7-year-old children. She was so subdued, lethargic, and apathetic that she seemed almost semistuporous. Her intelligence could not be evaluated at this time, because of her physical status. Later, when more careful examinations were possible, it was concluded that she was mentally retarded.

The vital signs were normal. The skin was thin and atrophic except over the lower chest, where there was a generalized desquamation. The appearance suggested an eczematoid eruption. There was a small ulcer on the left lower leg. Although the muscles were wasted, the extremities exhibited 4+ pitting edema and anarsarca was present. Some flaring in the epiphyseal plates at the upper end of both tibias was suggestive of rickets.

There was some frontal bossing. The distribution of the hair over the scalp was normal, but the texture of the hair was wiry and dry, and at the margin of the scalp, particularly at the ends of the hairs, a reddish tinge was evident. Cheilosis and minimal atrophic changes at the tip of the tongue were suggestive of a vitamin B_2 deficiency.

The abdomen was distended and tender, the tenderness being particularly referred to the umbilicus. Dilated loops of both large and small bowel could be palpated, and frequent peristaltic rushes were heard. The liver could be palpated 2 fingerbreadths below the costal margin. During the examination the child passed frequent semiliquid stools containing undigested food.

Laboratory Data.—Extensive laboratory investigations immediately after admission produced the following positive findings: The hemoglobin was 10 gm. %. There were 3,020,000 red blood cells

and 9270 white blood cells per cubic millimeter. Examination of the stools showed cysts and eggs of Ascaris lumbricoides, Trichuris trichiura, and Balantidium coli.

Clinical Course.—The child was seen by Dr. Grace Goldsmith,† who concluded that the diagnosis was kwashiorkor, complicated by multiple vitamin deficiences (A, B, and D and ascorbic acid). Immediate biopsy of the liver would have been desirable, to confirm the diagnosis, but the surgical staff declined to undertake it because the child was regarded as presenting too poor a surgical risk for any kind of operation.

On Dr. Goldsmith's recommendation, the patient was given a high-protein diet, consisting chiefly of milk and a concentrated vitamin supplement.

Vomiting and diarrhea continued intermittently through Jan. 9, the fifth day of hospitalization. Blood chemistry studies at this time revealed a serum protein level of 4.04 gm. %, with albumin representing 1.83 gm. and globulin, 2.21 gm. %. The icterus index was 11.7, and the serum bilirubin, 0.37 mg. %. The cephalin-flocculation test was negative. The thymol-turbidity value was 4.9 units. The child was not clinically jaundiced at any time.

On the 15th day of hospitalization she seemed generally improved and considerably more alert. Her weight had dropped to 35 lb., as a consequence of total disappearance of the edema present on admission. According to Dr. Derrick B. Jelliffe ‡ the large number of worms passed probably also played a part in the weight loss.

The electrophoretic pattern on the 17th day showed albumin 2.73 gm. %, α_1-globulin 0.34 gm. %, and γ-globulin 1.01 gm. %. On the twenty-first day studies of pancreatic function by duodenal intubation revealed the trypsin, amylase, and lipase levels to be slightly below normal.

On March 2, the 46th day of hospitalization, the child had fever (temperature to 101 F) and examination revealed bilateral parotitis. She was transferred to the contagious ward, but the diagnosis of mumps was later regarded as questionable, since the temperature elevation persisted only 24 hours and the parotid swelling disappeared within 3 to 5 days. Hemoagglutination inhibition tests were negative. It was therefore concluded that the condition was not mumps but the type of bilateral parotitis often associated with kwashiorkor.

On the 68th hospital day, although still with some reluctance, the surgical staff undertook biopsy of the liver. The liver was normal in size and appearance. A specimen 1 by 1 by 1.5 cm., taken from the right lobe, was reported by Dr. Charles Dunlap to show only minimal spotty periportal fibrosis and chronic inflammation. Sudan IV stain revealed an insignificant amount of fatty infiltration.

When the child was discharged, on the 77th hospital day, she weighed 42 lb.; this represented a 20% gain in weight (with due regard for the anasarca present on admission), although feeding had been a considerable problem. She was now 45.2 in. tall.

Follow-Up.—The child has been followed for four years. By July, 1955, her weight had increased from the 35 lb. recorded in the hospital in February, 1953, after the edema had disappeared, to 58½ lb. Over the same period her height increased to 51 in. In February, 1957, she weighed 61 lb., which was still well below the 3d percentile for her present age. There was still a reddish tinge to the hair. Intestinal parasites were still present. Biopsy of the skin of the abdomen showed local parakeratosis; there was no clinical evidence of dermatologic disease. Blood serology, all agglutinations, and serum protein and blood chemistry determinations were within normal range. The alkaline phosphatase was 13.37 units, and the bilirubin, 0.68 mg. %. Roentgenograms of the skull, chest, and long bones revealed no abnormalities.

Social History.—Several months before this child became ill, the father, for economic reasons, moved his wife and their 14 children from a farming community farther up on the Mississippi River to a sugar cane plantation 15 miles above New Orleans, on the west bank, in the hope of improving their economic condition. The hope was not realized.

The typical diet of the family on a weekday consisted of coffee and bread for breakfast, rice and beans for lunch, and bread, beans, and rice fried in lard for supper. On Sunday the diet included beef neck, cabbage and salt meat, or, occasionally, chicken. Fat meats were usually put in the pot daily for seasoning. Lard was the only fat used; butter was never served. Greens were cooked every two or three weeks. No fruit was ever eaten, and there were no vitamin supplements. The only sugar consumed was in small amounts in coffee and in the cane syrup in which the bread was sometimes soaked. Milk was available only during the summer. Then the children

† Dr. Grace Goldsmith, Professor of Medicine at the Tulane University School of Medicine and Director of the Division of Nutrition and Metabolic Diseases, is a member of the Committee of Protein Malnutrition of the Food and Nutrition Board of the National Research Council.

‡ Dr. Jelliffe, now Visiting Professor of Tropical Medicine at the Tulane University of Louisiana School of Medicine, is Consultant in Pediatrics to the World Health Organization.

received about a glass a week each, but this patient did not like milk and apparently never drank it. No cheese or other milk products were included in the diet. It was estimated that this diet is what the whole family had set before it, not what each individual member consumed. Undoubtedly, the father and mother, as the family breadwinners, received disproportionately more of it than did the children.

CASE 2.—A 4-year-old Negro girl, sister of the patient just described, was brought to Charity Hospital on Feb. 6, 1953, by the social service worker who was studying the home. In the preceding weeks she, too, had become drowsy and apathetic.

She weighed 17 lb. and was 31 in. tall, both figures being extremely low for her age. She sat apathetically but would walk if urged. The hair was jet black except at the margins of the scalp, where, particularly at the ends, it was reddish-gold. The skin was not remarkable except on the legs, where it was shiny and atrophic. Frontal bossing, cheilosis, and glossitis were present. The extremities, especially the legs, were small and poorly developed. There was slight general hyperreflexia. A rachitic rosary was present, and the abdomen was pot-bellied. The liver could be felt 1 fingerbreadth below the costal margin.

Blood studies showed hypochromic anemia (10.5 gm. % hemoglobin and 4,100,000 red blood cells per cubic millimeter). Ascaris and T. trichiura eggs were found in the stools. The albumin/globulin ratio was 4.4:3.6 gm. %. Roentgenograms of the skull and long bones showed a bone age of 1½ years. Studies of catheterized urine Feb. 10 and 11 (Table 1) showed that the child was not receiving a diet adequate in essential aminoacids or vitamins.

TABLE 1.—*Urinary Excretion Studies (Case 2)**

Substance	Daily Excretion 2/10/53	Daily Excretion 4/3/53
Nicotinic acid, mg.	0.9	1.89
N-methylpyridone, mg.	0.26	1.04
Tryptophan, mg.	2.1	7.1
	2.0	6.8
Nitrogen, gm.	1.2	3.69
Creatinine, mg.	52	170
Cyanocobalamin, μg.	22 †	26
	13	23
Folic acid, μg.	1.1	2.0
	0.8	
Citrovorum factor, μg.	1.8	0.8
	1.2	
Thiamine, μg.	129	856
	9.4	1,413
Histidine, mg.	19.4	Not calculated
	17.8	
Phenylalanine, mg.	6.4	Not calculated
	6.6	
Lysine	0	Not calculated

* These studies were made on a 24-hour catheterized specimen of urine (535 ml.). Normal values are not available, but the significance of this table is the difference between the very low values shortly after admission and the greatly increased values after several weeks of a proper diet. Two values indicate that two determinations were made. One or the other determination of thiamine is obviously incorrect, but it is impossible to say which one is in error.

† 1 μg. = 1/1,000,000 gm.

Liver biopsy was performed on Feb. 14. The only pathologic findings on microscopic examination were minimal areas of periportal fibrosis.

The patient was discharged on April 1, 1953, much improved after administration of a high-protein high-vitamin diet (Table 1). When she was brought back to the hospital in July, 1953, because of ascariasis, she showed continued improvement, but her weight and height were still below normal for her age.

When she was reexamined, in February, 1957, she was found remarkably small for her stated age of 8 years and was slightly retarded mentally. Many teeth were carious, but the frontal bossing, cheilosis, and glossitis originally present were no longer evident. Comparison of her hair with clippings secured in 1953 showed that the strands secured then were redder and straighter than the hair at this time. Dyspigmented hairs were still present at the margins of the scalp, but the color change was less marked. The rachitic rosary was still present. The skin over the extensor surfaces of the extremities was rough, dry, and xerotic. Serum protein studies were within normal range except for a slight increase in the β-globulin fraction.

CASE 3.—A 3-year-old Negro girl, another sister of the first patient in this series, was admitted to Charity Hospital on Feb. 6, 1953. She weighed 19½ lb. and was 30½ in. tall, both measurements being less than half of the normal for her age.

The skin was generally rough and dry, and a band of scaling dermatitis, thought to represent seborrheic disease, was present over the buttocks and in the diaper area. The ends of the hair were reddish, especially at the margins of the scalp. Slight photophobia was present. The gums bled at the slightest touch. Muscle tone was poor. A rachitic rosary was present, and the liver was palpable 1 fingerbreadth below the costal margin. The child exhibited the same apathy as the other children in the family.

The hemoglobin was 12 gm. %, and there were 3,050,000 red blood cells and 9250 white blood cells per cubic millimeter. Stool examination showed embryonal forms of T. trichiura and Endamoeba coli. The cephalin-flocculation test was 2+, but other liver-function tests were not definitely abnormal. Duodenal drainage showed lipase, amylase, and trypsin values at the lower limit of normal.

At laparotomy, Feb. 14, the liver appeared grossly normal. Histologic evidence of pathologic changes in the specimen secured was minimal.

TABLE 2.—*Urinary Excretion Studies (Case 3)**

Substance	Daily Excretion 2/10/53	Daily Excretion 4/3/53
Nicotinic acid, mg.	1.40	1.98
N-methylpyridone, mg.	0.39	1.23
Tryptophan, mg.	3.7	6.7
Nitrogen, gm.	1.46	3.48
Creatinine, mg.	112	120
Cyanocobalamin, μg.	84 27	73 37
Folic acid, μg.	0.8	3.2 28
Citrovorum factor, μg.	1.0	0.6

* See footnotes to Table 1. The total volume of urine was unfortunately not recorded in this study.

This child gained weight rapidly on a high-protein diet and was much improved when she was discharged, on April 5, 1953 (Table 2). When she was seen in July, 1954, she was still infected with intestinal parasites. When she was last observed, in November, 1956, she was of small stature for her age but was otherwise normal. She had a fringe of dry, lusterless, reddish-brown hair at the margins of the scalp.

CASE 4.—A 20-month-old Negro girl, of another family, was admitted to Charity Hospital on March 8, 1957. She was the eighth of nine children ranging in age from 10 years to 7 months.

This child, according to the mother, had been listless, lethargic, and losing weight for the past month, after vomiting and expelling worms periodically for some months previously. For a week her arms and legs had been swelling progressively, and there had been some abdominal swelling. There had been no abnormalities during the pregnancy or at delivery, and there was no history of previous illness. She had been breast-fed until the age of 13 months, when her 7-month-old sister was born and displaced her from the breast.

Physical Examination.—Physical examination revealed a somewhat malnourished, extremely apathetic child who was unable to walk, apparently from weakness. Muscle strength was poor. She showed little interest in the examination and made no outcry on venipuncture. Vital signs were normal. The weight was 22 lb., and the height, 30.8 in., both figures being under the 3d percentile for the patient's age. The hair was somewhat lighter in color than the usual Negroid hair and was sparse and dry. There was a slight rachitic rosary. The abdomen was pot-bellied, and the liver could be felt 1½ fingerbreadths below the costal margin. The most marked physical finding was a 2+ to 3+ pitting edema of the arms and legs. Neurologic examination revealed generalized hyporeflexia, which later cleared.

Laboratory Data.—The hemoglobin was 9.7 gm. %, and there were 4,090,000 red blood cells and 13,700 white blood cells per cubic millimeter. The reticulocyte count was 0.4 %. The sickle preparation was negative. The stool was heavily infected with ascarids. The initial electrocardiogram showed a prolonged P-R interval; later, this finding disappeared. The thiamine excretion test, following a load of 0.2 mg. per kilogram, showed an extremely low recovery rate in the urine. The serum protein level the day after admission was 3.6 gm. %, with an albumin-globulin ratio of 1.3:2.3. There was a mild hypokalemia of 3.8 mEq. per liter. Other laboratory data were within normal limits.

Clinical Course.—The child was placed on a half-skimmed milk diet supplemented by a multivitamin preparation. For several days she took little fluid by mouth, in spite of active efforts by the nursing staff to feed her. Antihelminthic therapy caused the expulsion of large numbers of ascarids over a period of several days.

Three days after admission the serum protein level had risen to 4.8 gm. %, with an albumin-globulin ratio of 2.19:2.61. Liver-function studies were not definitely abnormal. Roentgenograms of all bones showed marked osteomalacia, osteoporosis, and swelling of the soft tissues.

On March 12 the patient was presented to a combined pediatric conference, at which Dr. Jelliffe made the diagnosis of kwashiorkor on the basis of (1) edema, (2) mental apathy and lethargy, (3) retardation in growth, (4) diminished serum protein, (5) reversal of the albumin-globulin ratio, (6) ascariasis, (7) the social and dietetic history, and (8) the history of the patient as a "displaced" child.

On the day after the conference the edema began to subside. The child was still very weak, but she made an effort to walk. At the end of a week she was greatly improved. The stool specimens were still loaded with ascarids, however, and mild hypochromic anemia was still present. The protuberant abdomen had diminished in size, but the liver could still be felt 1½ fingerbreadths below the costal margin. On the 13th hospital day the serum protein was 4.96 gm. %, the albumin-globulin ratio being 2.78:2.18.

At no time during this child's hospitalization did she exhibit dermatologic findings typical of kwashiorkor. A mild scaling dermatitis was, however, present in the diaper area, and there was a small depigmented area in the left inguinal region.

At the time of writing (April, 1957) the child is continuing to improve on dietary therapy alone.

Social History.—The socioeconomic level of this family was low even by Charity Hospital standards. The father had deserted the mother shortly after the youngest child was born and had not contributed to the care of the children as directed

by the court. Meals, which consisted chiefly of gifts from neighbors, were irregular. The principal foods were red beans and rice, oatmeal, and dry cereal. Whatever milk was available was given to the 7-month-old baby. The patient had received almost none in the preceding six months. All the children in the family had intestinal parasites.

Essential Data on Kwashiorkor

Etiology.—Because of the wide distribution of kwashiorkor, in countries in which food habits are so widely varied, the etiology is not easily expressed in a sentence or two. Williams,[1] in her first cases, recognized the deficiency nature of the disease. By local food habits, children were given a thick paste or gruel made of maize as soon as they were taken off the breast, and she attributed the pathologic changes to some dietary association. She still believes that the disease is less frequent in areas in which rice or wheat forms the bulk of the diet than in areas in which such staple foods as maize and root vegetables (cassava and sweet potatoes) provide the bulk.

Although kwashiorkor is a deficiency disease, the lack is not in the vitamin components of the diet but in the protein elements. This condition differs from total undernutrition in that the intake of calories may be sufficient but the carbohydrate-protein ratio is at fault. Both the lack of protein and the excess of carbohydrates over protein do the damage.

Other factors are also important, particularly the proportion in which various amino acids do or do not appear in the diet.[4] Mukherjee and Jelliffee,[5] writing from Calcutta, pointed out that, just as repeated pregnancies and lactations may have a cumulative effect in the etiology of osteomalacia, it is possible that under similar conditions prolonged lactation in a poorly fed woman may result in decreased protein reserves. All of our patients were born of women who had had numerous pregnancies, and the reasoning seems highly logical.

It might be well to say at this point that, although the dispute still continues,[1] the best-informed opinion is that kwashiorkor is not infantile pellagra. Stannus, in 1934, advanced the opinion that they were the same disease, but, when both diseases are clear-cut, there can be no possibility of confusion. When they are less clear-cut, and particularly when they coexist, it may be hard to say which is more dominant.

In 1949 the Joint Committee on Nutrition of the Food and Agricultural Organization (FAO) and the World Health Organization (WHO) issued a statement to the effect that kwashiorkor is not identical with clinical pellagra and suggested that the name infantile pellagra should not be used for it.

Williams has made the distinction between the two conditions concisely and conclusively:

1. Kwashiorkor is common in young children, while pellagra is extremely uncommon in this age group.

2. When dermatitis is prominent in kwashiorkor, the disease is well entrenched. In pellagra, a severe dermatitis may appear before constitutional signs are apparent.

3. In kwashiorkor the rash has no relation to the exposed areas, while in pellagra the skin is photosensitive; the rash appears only on exposed areas and disappears when they are protected.

4. In the early stages of kwashiorkor the skin may be bleached and there is no well-marked edge to the rash. In pellagra, in the early stage of the rash, the skin is red, swollen, and irritated and the rash has a well-marked edge.

5. In the late stages of kwashiorkor the skin is dark, soft, and crumpled. It strips easily, and a raw surface is left. In similar stages of pellagra there is a dry, branny desquamation.

6. Kwashiorkor may develop in patients who consume some milk in their diets. Pellagra is not described in patients on a milk diet.

7. There is a large mortality in untreated kwashiorkor, while pellagra is not a common cause of death.

Organic Changes.—In Williams' first cases, as already noted, the mortality was high. Changes in the liver were the most important pathologic finding, and this has continued to be true of acute cases of the disease. In this type of case the liver is enlarged and the gross appearance suggests the presence of an enormous amount of fat. Histopathologic changes consist of fatty infiltration, fibrosis, and necrosis. In late childhood, however, there may be minimal demonstrable fat in the liver, as in our own cases, or none at all. The initial deposition of fat in kwashiorkor always follows this pattern: The fat is deposited first in the periphery of the lobule, after which there is progressive involvement of the cells toward the central vein.

Under treatment, the fat disappears. The explanation of the minimal findings in our cases in which liver biopsy was done is probably that the patients had been under treatment before it was undertaken. As a result, there was time for the fat to disappear or become minimal and for periportal fibrosis to develop. According to Dr. Jelliffee, complete reversion to normal is possible, under proper treatment, within a month.

An almost identical picture was induced experimentally by Hartroft and his associates [6] in rats subjected to cyclic protein feeding. The livers contained large fatty cysts and condensed periportal reticulin.

The masses of undigested food in the stools present in all stages of kwashiorkor, and at all ages, provide abundant evidence of failure of digestion. The acinar enzyme-secreting cells of the pancreas undergo intense acute atrophy while at the same time the secretory granules vanish and the cells are reduced to little more than nuclei, with a thin rim of surrounding cytoplasm. Normet [7] particularly stressed changes in the pancreas. This organ, together with the liver and the small intestine, has the greatest protein turnover of all body tissues and is thus peculiarly vulnerable to protein deficiency. Williams cited Davies' opinion that fibrosis of the pancreas is the primary lesion of kwashiorkor but did not state specifically that she agreed with him. Like the liver, the pancreas responds promptly to improvement in the diet, even if it is only moderate. Our first patient, who had large amounts of undigested food in the stools, had low values for trypsin, amylase, and lipase, even though the tests were made after 21 days of dietary treatment. In the third case these values were at the lower limit of normal.

Salivary Glands.—Atrophy of the salivary glands may occur in kwashiorkor but is not readily detected clinically in children, partly because of the abundant subcutaneous fat in this area and partly because of the edema associated with the disease. Microscopic examination, however, indicates that there is marked atrophy of these glands, due to shrinking and degranulation of the zymogen-secreting cells; the mucus-secreting cells, if they are involved at all, are less seriously affected. McCance,[8] in 1951, noted that swelling of the parotids has often been recorded after the refeeding of undernourished persons. His histologic studies in a single case led him to conclude that the increase in the size of the gland was due to an increase in the size of the individual acinar cells, which might represent functional hyperactivity of the enlarged parotid. He also concluded that this was a work hypertrophy, a response to overfeeding after a prolonged period of undernutrition. In view of the hepatic involvement in kwashiorkor, it is also interesting to note the recent study by Wolfe and his associates [9] in which cirrhosis of the liver in alcoholics was associated with swelling of the parotid gland.

In our first patient, as noted in the history of the case, bilateral parotid swelling ensued shortly after the diet was increased and improved. Although the condition was at first diagnosed as mumps, neither clinical

nor laboratory evidence supported this opinion and it seems reasonable to conclude that the involvement of the salivary glands was a manifestation of kwashiorkor.

Dermatologic Manifestations.—In mild cases there may be no definite dermatologic changes, though even at this stage there is likely to be a quality of dryness in the skin, with an increase in the deeper skin lines that goes on to fine desquamation. Large burnished areas of epidermis crack along natural lines, with little visible desquamation. We are not greatly impressed by this manifestation of the disease, as we find it in about a third of the children below the age of 6 years on the Negro wards of Charity Hospital; it is particularly evident on the legs. Many of the dermatoses observed in kwashiorkor begin in the diaper area in the inguinal folds, as in one of our own cases.

In advanced cases of kwashiorkor the skin changes are more conspicuous. Late in the disease there may be severe dyspigmentation, varying from bronze to reddish. In white-skinned children, according to Castellanos,[10] the first change is erythema, which blanches on pressure. This change is rapidly succeeded by small purple patches, which do not blanch; later they darken and have a waxy feel. They have sharp raised edges and well fit the name used for them, enamel-paint areas.

Clinically, enamel-paint changes first appear as blue-black-reddish spots varying from 1/16 to 1 in. in diameter. They are scattered over the body but are most numerous over the legs, thighs, buttocks, abdomen, scapular regions, arms, and forearms. Their appearance at first suggests petechiae, but careful study of these patients has failed to reveal any modification of the clotting time or capillary fragility, and there is no oozing when these areas are incised superficially.

Within two or three days these spots change from their original florid color to dark brown, reddish-brown, or black. They become dry, hard, scaly, and distinctly raised. Sometimes they resemble ecchymoses or lipoidoses. Fusion may occur. The skin becomes dark brown or black.

While new areas of enamel-paint dermatoses are developing at the edge of the original lesions, the central plaques enlarge. In acute cases, fluid collects below the outer layers of the skin and the appearance resembles that of a burn. Within a week, regardless of treatment, desquamation occurs. The pale thin epidermis which is exposed may ulcerate; if it does not, the exposed areas feel smooth and oily. In time, there is repigmentation of the depigmented areas of thin skin in which overlying enamel spots have been shed. Extreme skin changes occur only in terminal cases and seldom in areas subject to light.

Gillman[11] has nicely correlated the clinical manifestations of these enamel-paint spots with the histopathologic changes. The greatly thickened stratum corneum forms the elevation. Pigment particles, believed to be melanin or degradation products of melanin, are present in the lucidum-corneum complex. A stratum lucidum is seen in areas in which this zone is not usually observed.

In patients who recover, hyperpigmentation of traumatized areas is the rule. In advanced disease the skin is much more easily damaged than normal skin, especially over bony prominences. Children who suck their fingers may remove all the skin from them in the process.

Curiously, the dermatoses of kwashiorkor are painless, though perhaps this impression is due in some measure to the apathy these patients display.

Trowell and his associates[2] have observed that in some regions, such as Nigeria, the nails are sometimes soft and thin, though the changes are never marked. In Mexico, however, the nails are frequently very thin. When healthy new nails begin to grow, a mass formed at the nail base completely separates the new from the old nails.

Changes in the Hair.—Changes in the hair seem to vary with the regional loca-

tion of the disease. In India, Mukherjee and Jelliffee [5] found the changes minimal as compared with the rather striking changes seen in the disease in Africa. In the latter location hypochromotrichia was pronounced, the normal jet-black peppercorn curls often changing to straight, sparse, dry hair, varying in color from reddish-brown to gray. Our own patients, all Negroes, were born with the usual type of black Negroid hair, and the golden or reddish hue at the ends was therefore particularly striking.

Minimal changes in color involve the periphery and produce a so-called halo or fringe effect. The coloration may be light brown, reddish, golden, gray, or white. The evaluation of the changes must be made in relation to the norm of the particular racial group, and due attention must be paid to whether or not the hair is oiled; oiling tends to mask hypopigmentation. Relapse may be reflected by the presence of striped hair (*signo de bandera,* or flag sign).

The exact pathogenesis of the dyspigmentation is uncertain, although it seems likely that it is due to a breakdown in the normal process of melanogenesis. According to Gillman,[11] the explanation is partial depolymerization of melanin. Probably the crucial deficiency is in one of the sulfur-containing amino acids required for the production of tyrosine.

Before it is concluded that changes in the color of the hair are due to kwashiorkor, other possible causes must be taken into consideration, including genetic causes, racial admixtures, exposure to sun and wind, exposure to chemical dyes, and such chronic diseases as tuberculosis. Somewhat similar changes were observed by Chavarría and his associates [12] in Costa Rica. Infants and young children with severe avitaminosis, especially vitamin A deficiencies, as well as mixed avitaminic syndromes, pellagra, and nutritional edema, showed loss of hair, particularly in the frontal region, and dyspigmentation. Trowell and his associates [2] also pointed out that kwashiorkor is not the only disease in which a disturbance of protein metabolism is associated with changes in the hair; as examples, they listed kala-azar, hookworm, anemia, and cirrhosis.

Diagnosis

According to Williams,[1] the diagnosis of kwashiorkor, at least as the disease is observed in Africa, is made on the basis of the following manifestations:

(1) Retardation of growth.

(2) Dyspigmentation of hair and skin.

(3) Edema, usually associated with hypoalbuminuria.

(4) Pathologic changes in the liver, including fatty infiltration, fibrosis, and necrosis, alone or in combination.

(5) Nutritional dermatoses, which may be absent or may be present in a variety of patterns.

(6) Gastrointestinal disorders, which are variable but which may include, alone or in combination, anorexia, digestive upsets, diarrhea, and mild steatorrhea.

(7) Peevishness and mental apathy. According to Clark, mental apathy is the most important manifestation of the disease.

(8) A high mortality if the condition is untreated or incorrectly treated.

Williams mentioned one other point that it might be well to bear in mind. In her cases, all observed in equatorial Africa, coldness of the extremities was an important observation. Our own patients did not manifest this finding, or complain of it, but it is well to bear it in mind as one more possible link in the diagnostic survey.

In two of our cases studies of urinary nitrogen furnished important proof of protein malnutrition (Tables 1 and 2).

The differential diagnosis includes, in addition to pellagra, which has already been discussed, cirrhosis of the liver and carcinoma of the liver.

Treatment

In her second paper on kwashiorkor, Williams stated that the use of Nestlé's

tinned milk was curative in these cases. This was in 1935. She was of the same opinion in 1953. Other reports support her statement that if milk can be introduced into the diet it is almost curative without other therapy, provided that the disease is still reversible.

Skimmed cow's milk has been most frequently used in kwashiorkor. It is a convenient source of protein of high biologic value. Dried skimmed milk contains about 34% protein, and 150 gm. will provide the 50 gm. of protein which is needed daily in even a mild case. Animal proteins are more valuable than vegetable proteins, probably because they contain the methionine and lysine required for growth and not synthesized in the body.

Administration of the milk is not always as simple as it sounds, as at least one of our own cases proved. Small frequent meals should be given, with a high proportion of milk and, in the beginning, very little fat.

If the patient requires treatment urgently, the simplest way to administer the necessary protein is by repeated transfusions of packed red blood cells. Calloway and Mowrey[13] have produced some evidence to suggest that the excess of hemoglobin is broken down and transferred into serum protein.

Gillman and Gillman[14] have shown that the addition of riboflavin, nicotinic acid, thiamine, brewer's yeast, vitamin A, and vitamin D to the diet is not helpful and may be harmful unless these specific deficiencies exist. When they do, they require appropriate correction. Hansen and his associates[4] were able to show that a vitamin-free casein, water, glucose, and salt mixture could initiate a cure in kwashiorkor, as could synthetic amino acids. Vitamins helped, however, and the response was sometimes faster when they were given, but they were not essential. In these studies, the criterion of initiation of cure was improvement within 10 to 21 days after the special diet was begun. Two amino acid mixtures were tested. Although there was little difference in the clinical response, use of the 11-amino-acid mixture resulted in consistently lower nitrogen retention than the 18-acid mixture.

Treatment of associated diseases is naturally important. In every one of our own cases intestinal parasitism furnished a problem which was never solved.

Comment

The first and fourth of the patients described in this paper presented findings which are regarded as reasonably typical of kwashiorkor as it is observed in equatorial Africa, while the second and third patients presented milder forms of the disease. The first patient had continuous vomiting and diarrhea, with passage of semiformed stools containing undigested food; ascariasis; profound inanition; generalized edema associated with hypoproteinemia and anemia; clinical enlargement of the liver; a reddish tinge of the hair at the ends; apathy and mental retardation, and scaly, follicular skin changes over the chest. The fourth patient, a very much younger child, also suffered from vomiting, ascariasis, loss of weight, generalized edema, weakness, and pronounced mental apathy. Her hair did not show a reddish tinge but was lighter, sparser, and dryer than usual Negroid hair.

The second and third patients, sisters of the first, presented typical manifestations of the disease but in a milder (forme fruste) form. Profound inanition and apathy were particularly conspicuous. The scaly rash present over the buttocks of the third child seems similar to the changes observed in early kwashiorkor. The second of these children had the most marked reddish tinge to her hair, and this is still true, though the dyspigmentation is less pronounced at the end of four years than it was originally. Sections recently taken from the scalp were reported by Dr. Hermann Pinkus[15] to be fairly normal except for minor spotty lymphocytic infiltrates in the neighborhood of small hair follicles and

possibly unusual prominence of wide endothelium-lined lymph vessels.

In the three cases in which biopsy of the liver was undertaken, the histopathologic findings were limited to minimal fatty infiltration and periportal fibrosis. This is probably because, as already pointed out, the children had been under treatment before the laparotomies were performed and the hepatic changes were either completely reversed or well on their way to reversal.

All of these patients have improved with an improved dietary regimen, though they are still below normal in weight and height, particularly the first child described, whose physical and mental retardation is very evident. It is perhaps significant that she was the oldest of the four patients. The fourth child has been under observation too short a time to permit conclusions, but she has improved greatly on a high-protein diet.

Provision of food of high-protein and high-vitamin content by the Louisiana State Health Department has undoubtedly prevented a relapse of kwashiorkor in the first three of these patients. On the other hand, all of the children in the family, especially the younger ones, still eat dirt, and for this reason, plus their lack of cleanliness, intestinal parasitism still presents an unsolved problem.

The State Health Department, when it was observed that all of the children on the plantation on which the first 3 of these patients lived were smaller than normal, conducted a study on 68 of them in the summer of 1953, together with a feeding experiment.[16] Two-thirds were considered undersized and underweight. Some had rickets and scurvy. A high percentage were infected with intestinal parasites. None of them, however, presented the severe picture of nutritional deficiency exhibited by all three of the patients described. On the other hand, in at least three children there was noted a reddish tinge to the ends of the hair. It was not as pronounced in any case as in the three cases in the family described, but it is perhaps indicative of the existence in this locality of other cases of kwashiorkor of the forme fruste type.

Summary

Kwashiorkor, a protein-deficiency disease which was described definitively in 1933, was first observed in equatorial Africa and has since been reported in various parts of Asia, Europe, and Central and South Africa. The four cases reported in this communication from Charity Hospital of Louisiana at New Orleans are believed to the first reported in the United States.

Two of these cases, although the patients were acutely ill, were apparently milder than the variety of disease observed in Africa. The other two cases represent the forme fruste variety. All of the patients responded to correct (high-protein) therapy, but in one instance it was apparently instituted after certain irreversible changes had occurred.

It is believed that other patients in the United States are suffering from kwashiorkor, and it is hoped that this communication will call attention to the importance of recognizing and treating them.

Suite 1010, American Bank Building (12).

REFERENCES

1. Williams, C. D.: Kwashiorkor, J. A. M. A. 153:1280, 1953.

2. Trowell, H. C.; Davies, J. N. P., and Dean, R. F. A.: Kwashiorkor, London, Edward Arnold & Co., 1954.

3. Goldman, L.: Personal communication to the authors.

4. Hansen, J. D. L.; Howe, E. E., and Brock, J. F.: Amino-Acids and Kwashiorkor, Lancet 2:911, 1956.

5. Mukherjee, K. L., and Jelliffee, D. V.: Clinical Observations on Kwashiorkor in Calcutta, J. Trop. Pediat. 1:61, 1955.

6. Hartroft, W. S.: Personal communication to the authors.

7. Normet, cited by Trowell et al.[2]

8. McCance, cited by Trowell et al.[2]

9. Wolfe, S. J., Summerskill, W. H. J., and Davidson, C. S.: Parotid Swelling, Alcoholism and Cirrhosis, New England J. Med. 256:491, 1957.

10. Castellanos, cited by Trowell et al.[2]

11. Gillman, cited by Trowell et al.[2]

12. Chavarría, A. P.; Goldman, L.; Saénz-Herrera, C., and Cordero-Carvajal, E.: Canities and Alopecia in Children Associated with Avitaminosis: Preliminary Report, J. A. M. A. 132:570, 1946.

13. Calloway, N. O., and Mowrey, F. H.; Red Blood Cells as Source of Protein for Parenteral Use, J. A. M. A. 152:777, 1953.

14. Gillman and Gillman, cited by Trowell et al.[2]

15. Pinkus, H.: Personal communication to the authors.

16. Moore, M. C.; Rooks, E. P., and Peters, I. H.: Report on Supplementary Feeding of First Grade Children in a Central Louisiana Town, J. Louisiana M. Soc. 105:400, 1953.

ABSTRACT OF DISCUSSION

DR. ROBERT G. CARNEY, Iowa City: I should like to thank Dr. Henington for presenting this very interesting paper to the members of the American Dermatological Association and to congratulate him on introducing what is more or less a new disease, so far as the American dermatologic literature is concerned.

In listening to his paper two questions come to mind: First, what *is* kwashiorkor, and, second, do these two children have the disease? Neither question is easily answered. As to the definition of kwashiorkor, one can take the early work of Cecily Williams and haye a picture of severe protein deficiency associated with steatorrhea, edema, irritability, apathy, mental retardation, fatty infiltration of the liver, and certain distinct skin changes, these occurring in children recently weaned and often well-nourished calorie-wise. Death was almost certain once the skin changes were full-blown. Williams' studies were done on the Gold Coast of Africa. As other writers and other areas were heard from, the picture of kwashiorkor was both elaborated and rendered less definite, until, in 1955, we reach the paper of Gomez and co-worker, who present evidence that kwashiorkor, because of the steatorrhea and the pigmentary changes, is at most only a minor clinical variant of third-degree malnutrition. Gomez worked with Mexican Indians, I presume, and racial and dietary differences probably account for this minor variation.

Probably no deficiency disease is ever seen in pure form outside the laboratory. It is difficult to conceive that a child could eat a diet so deficient in protein without concomitant lack of vitamins, minerals, and other essentials. The literature on kwashiorkor reveals all sorts of combinations of the protein deficiency with other deficiency disease, particularly avitaminosis A, beriberi, pellagra, scurvy, and rickets, as well as infestations with worms, protozoa, and bacteria. As the clinical picture of kwashiorkor has developed over the past 30 years, nothing has suffered so much as have the cutaneous manifestations. Williams originally described a bizarre and classical lesion: The entire skin was of a muddy reddish hue, as was the hair; over the ankles, knees, buttocks, wrists, and elbows were black patches of soft, crumpled, thickened skin, these tending to spread over the extensoral surfaces; the central areas of these patches subsequently peel, leaving red, raw, denuded lesions. This picture is no longer considered essential to the diagnosis.

In this regard I should like to call to your attention a statement in the earlier works of Williams which has been ignored, it appears, either by oversight or because it was erroneous, and I have insufficient knowledge to render a judgment. She states that the muddy, reddish color of the skin and hair—the "dyspigmentation" often considered characteristic of the disease—is seen in many chronic debilitating diseases in the African Negro. If this is true, then one of the basic skin changes in kwashiorkor is nonspecific and diagnostically unimportant.

Current thought might allow the following definition: Kwashiorkor is a clinical syndrome associated with retardation of growth in early childhood, alterations in pigmentation of the skin and hair, edema, skin changes of various types, fatty infiltration of the liver early and periportal fibrosis later, anemia (usually normocytic), hypoalbuminemia, hypergammaglobulinemia, and a high mortality if untreated. Some would also add steatorrhea.

Dr. Henington presents two children who show edema with hypoalbuminemia, at least relative hypergammaglobulinemia, mild anemia, some evidence of hepatic damage, serious growth retardation, mental deficiency, apathy and irritability, and some skin changes perhaps compatible with the broad concept of kwashiorkor. Case 1, at 11 and 15, is far out of the age range for the syndrome. In three reports on kwashiorkor and third-degree malnutrition, covering well over 2000 cases, between 90% and 100% of the patients were in the age range from 6 months to 5 years. It seems that the children who do not die of the disease recover by the sixth year or soon after. Cases 2 and 3 lack many of the essential clinical and laboratory findings of kwashiorkor and third-degree malnutrition, the most important of which are the lack of characteristic serum protein picture and the fatty infiltration of the liver. The severe multiple infestations might be responsible for much of their trouble. Case 4 appears not to show the "dyspigmentation."

In my estimation, Cases 1 and 4 fit the picture of third-degree malnutrition. Whether one calls this kwashiorkor is probably a personal preference. Gomez would limit the use of the term kwashiorkor to those Gold Coast natives showing third-degree malnutrition with dyspigmentation, typical dermatoses, and steatorrhea. Cases 2 and 3 do not fulfil enough of the requirements to fit either third-degree malnutrition or kwashiorkor.

Since appalling conditions do exist in the United States, one can expect this syndrome to appear. Again, I congratulate Dr. Henington on calling it to our attention.

DR. ORLANDO CANIZARES, New York: I want to thank Dr. Henington for bringing this interesting case to our attention. We are extremely fortunate in this country that only two cases of this condition have been reported. It has been called the world's No. 1 pediatric problem, and in certain parts of the world one-half to two-thirds of all the children seem to be affected. This is especially true, of course, in the underdeveloped areas, where they receive a highly inadequate protein diet.

I had the opportunity to see several cases of this condition in Central America and in Colombia. They presented the clinical characteristics that have been described, especially the change of color of the hair, which is very striking. When you see little Indians with red hair, you become suspicious about the disease.

The diagnosis of this condition is relatively simple; in fact, the only difficult thing about the disease is the pronunciation of the name, and I will not even attempt it. As far as treatment is concerned, of course, the provision of protein gives a very satisfactory result, but the diet in those countries where the disease is common is usually made up of corn, rice, and beans. If no synthetic amino acids are given, the patients will continue to have this condition. Recently, the introduction of a peanut oil cake with fish flour, which has become rather popular in certain areas, seems to be solving the problem by giving the patient the needed protein.

DR. V. PARDO-CASTELLO, Havana, Cuba: This paper took me back to the years 1925 to 1935, the years of the depression, when we saw many of these cases among the Negro population of Cuba. This condition was first reported by our pediatricians about 1935 under the name of "pellagroid beriberi syndrome," which seems to me a more appropriate name than "kwashiorkor," which, as many of us have thought but few have said, does not mean anything to us.

The pellagroid beriberi syndrome has cutaneous changes, with symptoms similar to those of pellagra. The peeling of the skin, the redness, the increased pigmentation remind us of symptoms of pellagra, and, also, the chronic edema and the lack of interest on the part of the patient resemble the syndrome of beriberi as we used to see it, certainly in adult cases; so I should like to recommend the name "pellagroid beriberi syndrome."

The response of these children to treatment with vitamin B complex, and the proteins which they lacked for so many months and some of them for years, is very rapid. However, many patients died.

DR. MAURICE SULLIVAN, Baltimore: When Fitzpatrick returned from his recent trip to Japan, he described cases of phenylpyruvic oliogophrenia, or phenylalanine-deficiency disease, in the little dark-complexioned Japanese children. Their jet black hair had changed to red. Dr. Henington's patients certainly exhibit signs of a multiple deficiency of vitamins A, B, and D, minerals, and proteins. The striking pigmentary hair changes in Dr. Henington's patients could possibly be a manifestation of phenylalanine deficiency.

DR. CHARLES R. REIN, New York: Patients with this condition often show a reversal of the A/G ratio and may develop nonspecific serologic reactions for syphilis. I should like to ask Dr. Henington whether his patients were subjected to serologic examinations.

DR. V. MEDD HENINGTON, New Orleans: I should like to thank all of the discussers, and I shall try to answer as many of the questions as time will allow.

A controversy has been going on for years as to the difference between kwashiorkor and malnutrition. Many authors, including Dr. Gomez, who works in the Pediatric Hospital in Mexico, has stated that the conditions are one, and he criticizes the use of the word kwashiorkor and feels that it would be more appropriate to call this disease a form of malnutrition. However, many others disagree with this, and the World Health Organization has gone on record to say that kwashiorkor is an entirely different disease from malnutrition. In malnutrition one not only receives an inadequate amount of proteins but, in addition, receives an inadequate amount of carbohydrates and fats and therefore has a totally inadequate diet as to caloric content. In kwashiorkor these patients not only receive enough calories and carbohydrates but probably receive an abnormal amount. It is this abnormal ratio of carbohydrates to proteins as well as the lack of proteins that produces the clinical picture of kwashiorkor.

Dr. Pardo-Castello has brought up the possibility of this disease being infantile pellagra plus beriberi. When a child with kwashiorkor is given a load dose of vitamin B_1 plus nicotinic acid, which

should be curative for both beriberi and infantile pellagra, he does not improve and may die, if his diet is not supplemented by proteins.

Dr. Leon Goldman, of Cincinnati, has written me of some of the studies that he did on avitaminosis in Costa Rica, these were published in the *Archives of Dermatology and Syphilology* in 1946. He found definite hair changes in these children, but he did not find the other signs, such as low serum protein and liver damage, which seem to be necessary for the diagnosis of kwashiorkor.

Dr. Trowell, in his excellent book on kwashiorkor, reported his findings in 1145 cases which he reviewed; 45% of these children were between the ages of 2 and 3 years; however, he did report a group of patients up to the age of 20 years. So, as we see, age is no barrier in the diagnosis of this disease.

The Central Fixation Phenomenon

A Factor in the Prevention of Psychosomatic Skin Diseases

LEON GOLDMAN, M.D., Cincinnati

Those interested in the preventive aspects of the so-called psychosomatic skin reactions need to consider the central fixation phenomenon. This phenomenon has been seen before in instances of painful phantoms which occur after amputation. It is seen also in postherpetic neuralgia; here we have observed failure of relief of pain even with such vigorous peripheral measures as cord section. This same type of central fixation phenomenon can occur in chronic pruritic dematoses as a central fixation of "perceptability of itching."

In the analysis of the background of the persistence of chronic pruritic dermatoses there are certain phases to be considered. One is the local structural change in the skin which makes for continued stimuli of itching sensation. This structural change is associated with acanthosis, fibrosis, chronic inflammation, and local neural changes. These changes then can cause endogenous stimulation of the so-called itch point of Shelley and Arthur [1] in the skin. The inflammatory changes which occur about the nerve fibers in the skin may be either reversible or irreversible. When the inflammatory changes are severe and persistent over a long period of time, it is possible that these changes are not reversible. Such types of change are seen as irreversible lichenification persistent over a period of many years.

It is possible, also, that in addition to the local structural change in the skin there are changes in the enzymatic systems in the skin (endopeptidases?). To some extent, the proof of these disturbances would be in the changes observed in pharmacodynamic tests, as well as in histochemical studies. It is possible, also, that these enzyme-system changes may be reversible or irreversible from a functioning aspect.

In order to attempt to prove the presence of the central fixation phenomenon in chronic pruritic dermatoses, we have done the following types of experiments with so-called localized neurodermatitis, especially of the lower third of the leg and in the occipital areas. These areas are easily accessible; in many instances the area of involvement is not too large. This lichenified skin has been present for many many years. Our first experiments were with excision of a number of areas on the lower third of the leg in preparation for skin grafting. In two patients there was failure of relief of itching with deep excision. Both patients scratched off their skin grafts through the light surgical dressings; in one this occurred on the second postoperative day, and in the other patient, on the evening of the first postoperative day. Findings on biopsy of these patients showed lines of excision to be well below and around the chronic inflammatory changes. With the experience of these cases, plastic surgery was not recommended in such cases unless preliminary infiltration of these areas by local anesthetics abolished the itch sensation even for brief periods of time. The infiltration anesthesia was done by repeated injections of local anesthetics, chiefly by hypospray-jet injection, so that the entire area was infiltrated both superficially and deeply. Where the area was small, nerve

Submitted for publication Feb. 10, 1958.

From the Department of Dermatology, University of Cincinnati College of Medicine.

Presented in the Psychosomatic Dermatology Program, University of Cincinnati College of Medicine, Nov., 1957.

block was done by the anesthetist. With the persistence of itching in such areas after local anesthesia, it was assumed that there would be central fixation of the itching, and plastic surgery was not recommended.

In our experience, measures which make for vigorous cauterization of the skin in localized neurodermatitic patches have been ineffective for complete relief unless there was complete and deep removal of these patches. The techniques which we have employed include phenolization, undiluted tar painting, liquid nitrogen, and dermabrasion. We have used, also, occlusive bandages with both flexible latex-type bandages and skin casts. In addition, we have tried repeated injections of procaine and repeated intralesional injections of hydrocortisone and its newer analogs.

It is suggested that the same phenomenon of central fixation may account for the persistence of itching in chronic pruritic dermatoses much more extensive and widespread than the localized type of neurodermatitis. This would include, of course, atopic dermatitis (the generalized constitutional type of neurodermatitis), so-called generalized "secondary" neurodermatitis pruritus ani and vulvae, and psoriasis with secondary neurodermatitis. So-called "trigger areas" of pruritus in an extensive dermatitis can be identified by local infiltration techniques if the cooperation of the patient can be used.

It is true, also, that the physiologic changes in the skin, such as may be induced by tension, can also produce itch or even pain stimuli in the absence of any recognizable structural (or enzymatic?) change. These local changes induced initially cerebrally may also give rise paradoxically to the development of the central fixation phenomenon if they are repeated and continued often enough.

The prognosis of the central fixation phenomenon, if one can judge by analogy of the related painful phantoms and of the postherpetic neuralgia, is not good. Analysis, psychotherapy, tranquilizers, and local attempts to reduce the flow of stimuli from the skin show the difficulty of treating this disorder. It is possible, of course, if the central fixation phenomenon for such reactions as secondary localized neurodermatitis is not too severe and if the pattern can be interrupted for prolonged periods of time so that the patient gets continued periods of relief, that the central fixation phenomenon may be relieved.

From a prevention aspect, then, efforts to prevent the skin from becoming lichenified, from becoming continually "reactive," will do much to prevent the development of this central fixation phenomenon. The early and intensive therapy of the many facets of the background of atopic dermatitis in infancy and early childhood will help considerably. This should include preventive psychiatric programs, especially of the type which is done by those interested in the multiple mechanisms of atopic dermatitis. The excellent programs of Obermayer [2] and his colleagues and those done by Baer [3] are recommended for study and as example. The intensive continued therapy of mild flexural patches on the elbow and about the wrist and popliteal areas will also help. It is important to emphasize to these patients that the failure of these flexural areas, especially about the elbows, to tan during the summer is indicative of the persistence of atopic dermatitis even though the skin may appear to be of normal texture, may not be too reactive, and may not even itch. This type of whitened skin flares more readily in the fall and winter than does the skin which reacts normally to sun tanning. This is a small but practical point in the prevention program of this chronic disorder.

The early attention, in young people especially, to psoriasis or neurodermatitic patches about the lower extremities, about the vulva and rectum, and in the occipital area will also help in the prevention of these disorders in those areas. When so-called localized neurodermatitis occurs in these vital areas, even though it may not be too uncomfortable, it must continue to

receive intensive treatment, especially for the relief of pruritus.

Summary

A central fixation phenomenon similar to that which does occur in painful amputation phantoms and in postherpetic neuralgia may develop also in chronic pruritic dermatoses. The prognosis is worsened by the presence of such a phenomenon. Attempts should be made to prevent the development of such a reaction by the early and intensive therapy of all of the phases of chronic pruritic skin disorders.

University of Cincinnati (21).

REFERENCES

1. Shelley, W. B., and Arthur, R. P.: The Neurohistology and Neurophysiology of the Itch Sensation in Man, A. M. A. Arch. Dermat. 76: 296, 1957.

2. Rush, S.; Storkan, M. A., and Obermayer, M. E.: Neurodermatitis and Emotional Tension, A. M. A. Arch. Dermat. 76:766, 1957.

3. Baer, R.: Current Views on Atopic Dermatitis, New York J. Med. 56:1664, 1956.

The Problem of Syphilis Today

HERMAN BEERMAN, M.D., Philadelphia

It is fitting on this occasion to discuss a subject which was dear to the heart of Dr. Charles R. Rein, whose memory we are here to honor. For many years, Dr. Rein expressed concern that, in spite of great advances, syphilis would sooner or later recrudesce to a major problem. It is, however, becoming increasingly apparent that syphilis, in spite of these fears, is rapidly taking a place of less importance in medical practice; in fact, some investigators believe that the diminution of syphilis incidence is so great as to make it an uncommon or even rare disease, a situation which these persons feel will be permanent. It would now appear, as Moore [1] has stated, that the venereologist (syphilologist) finds himself in the position of having worked himself out of a job. This decreased incidence of syphilis has resulted in decreased appropriations for its control. Thus, since there is no adequate appropriation for finding syphilis, none is found. This leads to the false idea that there is no syphilis and, therefore, none needs to be taken care of (obviously an ostrich attitude). This false confidence has been well put recently by Ambrose King in his presentation, "These Dying Diseases." [2] Suspension of publication of good American sources of information on syphilis and the other venereal diseases and the dropping of "syphilology" from the titles of departments of dermatology in many medical schools and from the names of well-established societies are all signs of the times. Undoubtedly, penicillin therapy has played no small role in this decline of syphilis and the interest in it as a disease. It is contended that since penicillin treatment is so safe and effective the fine points of diagnosis and differentiation of syphilis from other diseases may be dispensed with and that no harm will come from the wholesale, almost indiscriminate use of the drug. Already, the effects of this philosophy are becoming apparent. Penicillin is capable of causing reactions, even fatal ones. Certain patients with syphilis actually go through various clinics, including dermatology, without the nature of their disease being suspected for some time. The result also is that medical students have no opportunity to learn about the diagnosis of this disease. Failure to employ serologic tests for syphilis leads to loss of diagnostic advantage in early lupus erythematosus. In addition, here and there actual increases in the syphilis population are noted, while in general there is a definite sustained reduction in the incidence of this infection up to a certain point. Although many advances have been made, there are still numerous unanswered problems connected with syphilis as well as with the other treponemal diseases. Despite the progress made in reducing the mortality from syphilis, it still remains one of the more important causes of death among infectious processes. Notwithstanding the great advances, one must keep in mind Neisser's [3] dictum, "Human indolence and stupidity will arrange that syphilis will never die out but will remain always a dangerous dis-

Submitted for publication Feb. 26, 1958.

Read before the Bronx Dermatological Society, Dec. 19, 1957, in a symposium held in memory of Dr. Charles R. Rein and entitled "Syphilis and Related Treponematoses in the World Today."

From the Departments of Dermatology, University of Pennsylvania Graduate School of Medicine and University of Pennsylvania School of Medicine. Professor and Chairman, Dermatology, University of Pennsylvania Graduate School of Medicine, and Professor of Dermatology, University of Pennsylvania School of Medicine.

ease, but we know that new weapons have been placed in our hands to combat it." This statement made almost 50 years ago, when the great "magic bullet" arsphenamine (Salvarsan) was introduced, has been reiterated several times since, always with great hope for the future but admittedly never attaining such strides in the control of syphilis as we have had since penicillin. Nonetheless, in spite of all that has been said, syphilis is still a problem to be contended with. In this discussion I shall indicate that syphilis is recurring in many places all over the world, although the net result is still to the good. Because penicillin has made it for the first time possible to cure syphilis,[4] our attitude toward this problem has been somewhat changed. Likewise, the question of relapse and reinfection needs further elucidation. Thus, 13 years after the introduction of penicillin, I shall discuss briefly the following questions: What has penicillin done? Is syphilis dead? What is the evidence for or against this? What are still problems in syphilis, and what is the future of syphilis?

The contention that syphilology has become rather unimportant goes back a number of years, but in 1950 Dennie[5] discussed this under the heading "The Dying Syphilologist." He concluded that "the syphilologist may be dying, but syphilis is not." The passing of the diagnosis and management of syphilis from the hands of a few, usually dermatologists, to physicians in general is more apparent now than it has been in the past. This trend, of course, carries with it an obligation of which the practitioner may well be cognizant. This includes careful examination before therapy and careful post-treatment follow-up study, as well as case finding, if the best interests of the public health are to be served. Rosahn's[6] study of the adverse influence of syphilis on longevity has given practitioners something to think about. All of this did not deter organizations from manifesting a lessened interest in syphilis or the other venereal diseases to the point that a belief swept the community that these diseases no longer constitute a danger to society or a challenge to medicine. This was due to publicity, to a steady decline in the early manifestations of the once fulminating disease syphilis, and to the effects of therapy with arsenicals and penicillin, which in turn have done much to modify the disease and to set up further waves of optimism. It was felt about four years ago that the shortcomings of therapy were developing a reservoir of late infection and that penicillin was creating an early stage of latency in syphilis. In certain quarters,[7] however, the venereal disease hunt was still on and substantial gains in reducing the incidence rate of syphilis were being made. (Gonorrhea is declining at a much slower rate than that of infectious syphilis.) Thomas[8] likewise discussed this problem. He stated that, like most relatively sudden and dramatic changes, the unprecedented decline in the reported cases of syphilis in recent years has produced undue optimism in some quarters and unjustified skepticism in others. It would be unrealistic to predict the swift eradication of a disease as complex in its clinical and epidemiological aspects as syphilis. Yet the statement "the long-term trends in the incidence of syphilis have not been altered by antibiotic therapy" would be almost equally unrealistic. Over 200,000 previously unreported cases of syphilis were reported in this country in 1951. During the same period, 3500 cases were found in upstate New York. The fact that only 10% of newly reported cases were in the primary or secondary stages is an indication of difficulty in controlling this disease. There was an 80% decline in the number of cases of infectious syphilis in upstate New York in 1951 compared with the annual average of the five years preceding World War II. It is also the belief among physicians dealing with syphilis that there is less symptomatic syphilis than at any other time in

the history of the nation. The anticipated postwar decline in syphilis rates and the reduction in the virulence of the organism during the last century cannot explain the recent gains. The antibiotics must have played an important role. Penicillin is greatly superior to any previously known antisyphilitic agent. Without the efforts of the public health departments, however, penicillin or its predecessors could not have produced the present unprecedented drop in syphilis. Research in various departments, particularly in the New York State Department of Health, resulted in newer stimulation for investigation of serologic testing. As a result of the progress, many of the syphilis clinics in upstate New York have been closed. Treatment of syphilis has been turned over to the private physician. Thomas felt that within the decade after 1953 late symptomatic syphilis would be as rare at typhoid. There is, however, another side to this story. Certain trainees in dermatology and syphilology have not only failed to recognize active syphilis but have actually neglected to consider this disease in differential diagnosis. Furthermore, some editorial accounts in medical and lay journals of the potential national resurgence of syphilis are indications of how critical present need for knowledge about syphilis is. For example, an article in the *Ladies' Home Journal*[9] spoke of "The Dread Comeback," and *Time* magazine,[10] reporting the proceedings of the 1953 meeting of the American Academy of Dermatology and Syphilology Symposium on Syphilis, of which Dr. Rein was the Chairman, stated: "It looked as though syphilis no longer required the services of specialists or even much attention. Some hospitals reported difficulty in getting enough cases for long-term research. Before the week was well along, the specialists changed their minds. Syphilis, they heard, had gone down for a count of nine but is now up and swinging again." *The Journal of the American Medical Association*[11] stated editorially that venereal disease control is not automatic and pointed out that although there was a downward trend in cases of primary and secondary syphilis this may mean either fewer cases or failure to find new cases. Every year the number of reported cases of early latent syphilis has exceeded that of primary or secondary syphilis. This indicates that more than half of the cases of syphilis go into the late phase before being discovered. The editorial further states that, although great strides have been made in venereal disease control, complete control is far from being accomplished. A study by Lentz and Beerman[12] in 1952, in which a questionnaire was mailed to 4236 physicians practicing in Philadelphia, indicated that if all patients treated had been reported there would have been an increase of almost 60% in syphilis and 70% in gonorrhea incidence in the records of the Philadelphia Department of Health. Furthermore, only 7% of the physicians had treated over 70% of the patients. Moore[1] noted in an editorial that fresh infections of syphilis reached a near-epidemic peak in 1947 and then began a drop. The decrease in incidence by 1952 amounted to nearly 90% of the peak incidence. Despite this decline, the internist may encounter diagnostic and therapeutic problems of late syphilis for a generation to come. The peak of discovery of congenital syphilis was in 1941, with a progressive fall to 1952. Likewise, the *British Journal of Venereal Diseases*[13] states that, although there was about 8% increase in both male and female cases of gonorrhea in the second quarter of 1953 as compared with the first quarter of that year, the downward trend of early syphilis continues uninterrupted, albeit at slackening tempo, and the number of cases of late syphilis remains essentially unchanged. Factors such as the untraced contacts of persons with late syphilis and the defaulting early syphilitics, which constitute a hard core of patients with early syphilis, make it obvious that the venereologist still has much to do to

control venereal disease and its effects. Reduction in clinic facilities and control efforts at this time would be of little direct economy and would actually indirectly cost the country (British Empire) dear.

Syphilis (and the other treponematoses) still are an important world public health problem.[14] It was estimated in 1955 that there were about 20,000,000 persons with syphilis in the world and that in special areas of certain countries as many as 80% of the population were probably affected. There was wide variation, of course, within countries in the prevalence of venereal disease. In Africa as a whole it ranged from 14.1% to 32.9%; in southeast Asia, from only 0.6% to 31%; in Egypt, from 0.29% to 27%; in India, from less than 1% to 50%.

In 1955 Rein[15] regretted the lowered index of suspicion on the part of physicians who believed that venereal disease may be eradicated if proper measures were taken. Already in 1955 in some areas of the United States the clinical incidence of early infectious syphilis was no longer falling, and in 1956 the Third Annual Joint Statement of the Status of Venereal Disease Control in the United States[16] continued to urge increased Federal support of state and local venereal disease control programs, increased attention on the part of the Federal Government to venereal disease problems of migrant labor, collection of information and development of a program to prevent venereal disease among teenagers, and Congressional appropriation of $5,000,000 for Federal assistance to states. At present, there still seem to be more conflicting data with respect to the incidence of syphilis and the need for its control, one group reporting a falling trend and the other maintaining that syphilis is still here. In the past year, however, certain evidence indicates that syphilis has not been conquered. For example, in New York City, Rosenthal and Vandow[17] indicated that although the number of newly reported cases per 100,000 population in 1954 was about half of what it was in 1938, there were still about 20,000 newly reported cases that year. In fact, in the United States as a whole, 156,000 new cases of syphilis were reported in 1953. Although it is true that the number of cases of congenital syphilis has significantly decreased, there has been a much more gradual fall in the incidence rates of early, late latent, and late syphilis. Further reductions in incidence of venereal disease will be difficult to achieve in an area such as New York City, which is not only a focal point for traffic from all parts of the United States but also is a global seaport and airport. Population movement from within the country combined with increasing international traffic constitute problems beyond any local public health control. These and other factors peculiar to a large metropolis indicate the need for maintaining a vigorous program for the continued control of venereal disease. Likewise, Vought et al.[18] consider the control of syphilis in the state of New York to be far from an accomplished fact. In order to induce a continued downward trend, these two aspects of control are emphasized: systematic efforts to locate the population groups most at risk of acquiring the disease by intensive epidemiologic studies and intensified control procedures in the groups thus located. A report of the North Carolina Venereal Disease Control Section[19] indicates a small decline in 1954, although the total treatment activity was increased because known contacts of persons with gonorrhea and syphilis were treated on a prophylactic basis. There were two major venereal disease epidemics, involving 75 persons in Chadbourn and 127 in Greensboro. Fiumara and his associates[20] reported an outbreak of syphilis and gonorrhea in Massachusetts. Schamberg[21] reports that the rate of new syphilitic infections in the United States decreased by 93% between 1947 and 1954. Factors which have brought about this reduction, however, do not assure continued decline;

periodic epidemics will remain a possibility until a method of immunization is developed. Porter [22] claims that in the state of Delaware there has been an increase in the reports of new infections since 1952. He stated that there must still be a sizeable reservoir of cases which have not been detected or adequately treated. He feels that the battle against syphilis is not yet won. Some increases in the incidence of syphilis have been noted in Ohio, by DeOreo,[23] and in New Jersey,[24] especially in the teen-agers. Parker,[25] of Nebraska, while recognizing the decreased total incidence of syphilis, feels that the venereal disease problem has not been solved. He, too, calls attention to the increase in venereal diseases among teen-agers. Dennie [26,27] thinks that both the medical profession and the laity must be reacquainted with the fact that syphilitic disease is still a formidable factor in the list of contagious diseases in our country. Millions of people are still suffering from this disease. New cases run into the hundreds of thousands each year. In order to control syphilis and gradually eliminate it as an important factor in the health problem of the United States, a system of education must be carried on not only continuously but more intensely. Similarly, Touraine [28] is opposed to any relaxation in the campaign against venereal disease. He believes that penicillin is not the only factor involved in the decline of venereal disease (syphilis). There are well-known cyclical fluctuations in the prevalence of these diseases. Therefore, early serological and clinical detection of unrecognized and latent cases and social measures against infections from home and abroad remain important. Crandell and his associates [29] conclude, from a survey of private patients and one in a psychiatric hospital, that in view of the number of patients with syphilis of the nervous and cardiovascular systems in a single institution "Syphilis is Still Here." Fiumara, Appel, Hill, and Mescon,[30] who have reviewed the present status of syphilis and its management, reiterate that the venereal diseases are on the rise again and that syphilis is still a nationwide problem. This means that a reservoir of infectious syphilis exists in most communities. There is also a residuum of noninfectious syphilis. All of these data indicate that syphilis will be a serious medical problem for many years. In Pennsylvania [31] a 13.4% increase in the number of new cases of venereal disease was reported for the state in 1956 as compared to 1955. The *British Journal of Venereal Diseases* made a survey of the leading venerologists in many countries to outline the current venereal disease status in their countries. Great Britain reported the first rise in the number of new syphilitic patients since 1947. In Canada, as well as in Australia, an over-all decline in syphilis incidence was noted. Durel [32] reported from France that there, as in many other countries, early syphilis had been reduced by over 90% from 1945 to 1955 but that gonorrhea, including urethral discharges of all types, had been reduced by only 50%. Sweden has noticed a decrease. In Norway the situation is satisfactory. In India, Rajam [33] reported that syphilis still ranks high as a major public health problem. In spite of this generally satisfactory situation, an editorial in the *New England Journal of Medicine* [34] points out that here and there small epidemics of syphilis were reported during the fiscal year July 1, 1955, to March 31, 1956. More cases of primary and secondary syphilis were reported in the United States than in the corresponding period of the previous fiscal year. The indications are that the control effort is unable to cope with the national problem of syphilis. Since the increases in both sexes were found in 20 widely scattered states among both Negroes and whites and were characteristic of both private and public treatment sources, they may well forecast large increases in infectious syphilis throughout the nation. Massachusetts, an area of low syphilis population, had a

20% increase in syphilis in 1951, principally in the late and latent phases. These reported rates continued without significant changes at this elevated level until the present fiscal year, when another and sharper increase was noted. There was a 59% increase in primary and secondary syphilis and a 14% increase in early latent cases over the previous year, making an over-all increase of 30% in infectious syphilis. Late latent and late syphilis increased by 17%. The years of complacency are bearing bitter fruit. In the Fourth Annual Report [35] on venereal disease problems and programs it is contended that states, territories, and cities cite no substantial improvement in their programs over last year and a definite worsening of the venereal disease picture in selected areas for the country as a whole is claimed. This report was prepared by three national organizations and is based on separate reports from all 48 states, from 3 territories, and from 94 of the 109 cities in the United States with populations of 100,000 or over. It was revealed that rates are rising statewide in 19 states, that control programs are inadequate in 35 states, that teenage venereal disease is increasing in 11 states, that new epidemiologic outbreaks are reported in 19 states, and that Armed Forces personnel, transient laborers, and other mobile groups are listed by 32 states and 15 city health officers as major problems in venereal disease control.

Moore [36] believes that syphilis may never be eradicated but that substantial progress has been made and the trend is downward. He feels that epidemiologic facts do not support the view that recent optimism has been disastrous. Only continued vigilance will maintain the gains. In 1956 Perry and his co-workers [37] at the Mayo Clinic felt that the problem of syphilis today is chiefly concerned, in the absence of early syphilis, with the evaluation of positive serologic tests for syphilis.[38] While they recognize the great drop in the incidence of syphilis generally speaking, they are of the opinion that because of the infrequency of seeing clinical syphilis this disease is omitted for consideration in the differential diagnosis of patients with obscure signs and symptoms. It would appear that the disease is by no means eradicated, and physicians and public health officials must be ever alert to the possibility that syphilis may still produce disability, financial ruin, dementia, and death.

In a recent communication, Rein [39] summarized the syphilis problem of today. He stated that syphilis is on the rise again. A Public Health Report estimated that 1,921,000 persons in the United States have syphilis requiring treatment. Many states and large cities find their venereal disease appropriations inadequate to permit an effective and progressive program. Of major concern is the fact that high rates for primary, secondary, and early latent syphilis are in the age group of 15 to 19, reaching a peak at the 20- to 24-year group. Rapidly declining rates over the past several years have prompted the optimistic demobilization of venereal disease control forces, reassignments of personnel and reduction of case findings, and reduction of diagnostic and treatment facilities, leaving many areas without means to discover cases or to combat sudden outbreaks. Rein crystallized the essence of the present problem of syphilis when he stated that as physicians "we have the diagnostic tools and the therapeutic agents to control and even eradicate syphilis. But we are failing because of our own complacency about the disease, because of neglected educational programs, especially for the teenagers, and because of lack of interest or funds to find and treat the affected persons."

255 S. 17th St. (3).

REFERENCES

1. Moore, J. E.: The Changing Pattern of Syphilis 1941-1953, Editorial, Ann. Int. Med. 39: 644-649 (Sept.) 1953.

2. King, A.: These Dying Diseases, Lancet 1: 651-657 (March 29) 1958.

3. Neisser, A.: On Modern Syphilotherapy with Particular Reference to Salvarsan, translated by Isabelle von Sazenhofen Wartenberg, Baltimore, The Johns Hopkins Press, 1945.

4. Urbach, E., and Beerman, H.: The Present Status of Immunity and Allergy in Syphilis, Am. J. Syph. 31:192-215 (March) 1947.

5. Dennie, C. C.: The Dying Syphilologist, Arch. Dermat. & Syph. 62:615-621 (Nov.) 1950.

6. Rosahn, P. D.: Adverse Influence of Syphilitic Infection on Longevity of Mice and Men, A. M. A. Arch. Dermat. & Syph. 66:547-568 (Nov.) 1952.

7. Bauer, T. J.: The VD Hunt is Still on: Continued Decline Needs Continued Control, J. Social Hyg. 38:290-296 (Oct.) 1952.

8. Thomas, E. W.: The Problem of Syphilis Control, Health News, Albany, N. Y., New York State Department of Health 29:3, 1952.

9. Sontheimer, M.: The Dread Comeback, Ladies' Home Journal 71:38-39 (July) 1954.

10. Up from a Count of Nine, Time 62:71 (Dec. 21) 1953.

11. Venereal Disease Control is Not Automatic, Editorial, J. A. M. A. 155:911-912 (July 3) 1954.

12. Lentz, J. W., and Beerman, H.: The Treatment of Venereal Diseases in Private Practice in Philadelphia, Am. J. Syph. 37:427-438 (Sept.) 1953.

13. Venereal Diseases, the Changing Problem, Editorial, Brit. J. Ven. Dis. 29:197 (Dec.) 1953.

14. Guthe, T., and Willcox, R. R.: Treponematoses, A World Problem, Geneva, World Health Organization, 1954.

15. Rein, C. R.: Chemotherapy of Syphilis and Gonorrhea, Editorial, Antibiotic Med. 1:4 (Jan.) 1955.

16. Today's V. D. Control Problem: A Joint Statement to the Appropriation Committee of the Federal Congress, 1954, Am. J. Syph. 38:161-175 (May) 1954.

17. Rosenthal, T., and Vandow, J. E.: Venereal Disease Control in New York City, Pub. Health Rep. 71:381-390 (April) 1956.

18. Vought, R. L.; de Mello, L., and Locke, F. B.: The Decline and Fall of Syphilis in New York State, J. Chron. Dis. 2:303-310 (Sept.) 1955.

19. Departmental Reports, North Carolina State Board of Health, Jan. 1, 1954-Dec. 31, 1954, Health Bull., pp. 7015-7036, 1955.

20. Fiumara, N. J.; Shinberg, J. D.; Byrne, E. M., and Fountaine, J.: An Outbreak of Gonorrhea and Early Syphilis in Massachusetts, New England J. Med. 256:982-990 (May 23) 1957.

21. Schamberg, I. L.: Can the Treponeme Stage a Comeback? A. M. A. Arch. Dermat. 73:523-529 (May) 1956.

22. Porter, W. L.: The Battle Against Syphilis Is Not Yet Won, Delaware M. J. 27:212-214 (Sept.) 1955.

23. DeOreo, J.: Is Syphilis Still a Problem? Bull. Acad. Med. Cleveland 42:14 (July) 1957.

24. New Jersey Reports Teen VD Increase, Social Hyg. News 32:3 (Sept.) 1957.

25. Parker, S.: Venereal Disease Control in Nebraska, Better Health, Lincoln, Neb., Nebraska Department of Public Health 16:4 (Sept.-Oct.) 1957.

26. Dennie, C. C.: What About Syphilis? Missouri Med. 52:785-786 (Oct.) 1955.

27. Dennie, C. C.: Syphilis—A Vanishing Disease, Mississippi Valley M. J. 75:101-105 (July) 1953.

28. Touraine, A.: Doit-on atténuer la Lutte antivénérienne? Presse méd. 63:1067-1068 (July 23) 1955.

29. Crandell, C. A.; Melvin, D., and Abraham, A.: Syphilis is Still Here, J. M. Soc. New Jersey 53:118-119 (March) 1956.

30. Fiumara, N. J.; Appel, B.; Hill, W., and Mescon, H.: Syphilis and Its Management: A Present-Day Problem, New England J. Med. 254: 1127-1130 (June 14); 1173-1178 (June 21) 1956.

31. The Pennsylvania Public Health Association Vol. 5, No. 3, Sept. 1, 1957.

32. Durel, P.: Survey of the Venereal Disease Situation in France, Brit. J. Ven. Dis. 32:145-149 (Sept.) 1956.

33. Rajam, R. V.: Venereal Diseases in India, Brit. J. Ven. Dis. 32:79-81 (June) 1956.

34. Syphilis Resurgent, Editorial, New England J. Med. 255:357-358 (Aug. 16) 1956.

35. Today's V. D. Control Problem: A Joint Statement by the Association of State and Territorial Officers, New York, The American Venereal Disease Association and the American Social Hygiene Association, 1957.

36. Moore, J. E.: The "Rising Tide of Infection" of Syphilis, J. Chronic. Dis. 6:280-283 (Sept.) 1957.

37. Perry, H. O.; Kierland, R. R., and Magath, T. B.: The Clinical Problem of Syphilis Today, Minnesota Med. 39:717-722, 736 (Nov.) 1956.

38. Beerman, H.: Significance of a Positive Serologic Test for Syphilis, GP 16:79-84 (Sept.) 1957.

39. Rein, C. R.: The Present Status of Syphilis, New York J. Med. 56:2563-2566 (Aug. 15) 1956.

An Effective Simplified Serologic Test for Syphilis Employing Reiter Protein

GEORGE H. KOSTANT, M.D., and LOUISE C. KELCEC, M.T., New York

The ideal serologic test for syphilis would be one which satisfies certain practical and logical criteria. It should give positive reactions with the serums of all patients with a syphilitic infection; it should give negative reactions with the serums of nonsyphilitic persons; furthermore, it should be relatively inexpensive and simply performed by the average hospital laboratory. Unfortunately, such an ideal test is not available. Theoretically, a test employing cultured pathogenic Nichols strain Treponema pallidum as an antigen could be expected to fulfill these criteria. To date, however, the cultivation of this micro-organism has never been realized, despite the efforts of Noguchi [1-3] and others. In an attempt to culture this treponeme Nelson [4] devised a medium which is capable of maintaining the life of the virulent Nichols strain T. pallidum for as long as 14 days with a half-life of 6 to 8 days. Unfortunately, even this culture medium does not favor the active multiplication of this micro-organism, which requires living animal tissue for its growth. For this reason, the treponeme of syphilis must be harvested from rabbit testicular syphilomas to serve as the source of the antigen employed in the T. pallidum immobilization (TPI),[5] the T. pallidum immune adherence (TPIA),[6-8] and T. pallidum complement-fixation (TPCF)[9] tests.

In the TPI test, living motile micro-organisms are employed to demonstrate the immobilizing antibody. While this procedure has become widely accepted for the differentiation of true from nonspecific serologic reactors, there are certain drawbacks to its use. Since living treponemes are employed, it is necessary to maintain a colony of animals from which these micro-organisms are harvested. There is, therefore, always the potential danger of accidental inoculation with syphilis of laboratory workers. Serums examined with this test procedure must be collected and handled with sterile precautions. Moreover, the presence of penicillin or other treponemicidal antibiotics in the serum interferes with the test. In addition, its performance is difficult and time-consuming and requires the tedious counting of spirochetes with the dark-field microscope. These reasons together with the high cost of the antigen make it obvious that the TPI test is not suitable for mass testing.

In contrast to the TPI test, the TPIA test employs killed treponemes as an antigen, and this antigen may be stored under refrigeration and distributed to small serology laboratories. The principle of the TPIA test is the adherence of the nonliving micro-organism to human red blood cells in the presence of syphilitic antibody and active complement. In a positive test the treponemes are absent from the supernate because they are attached to the red blood cells in the sediment. While the employment of dead treponemes eliminates some of the problems connected with the use

Received for publication March 1, 1958.

Read before the Bronx Dermatological Society, Dec. 19, 1957, in a symposium held in memory of Dr. Charles R. Rein and entitled "Syphilis and Related Treponematoses in the World Today."

From the Department of Dermatology and Syphilology of the New York University Post-Graduate Medical School (Dr. Marion B. Sulzberger, Chairman) and the Skin and Cancer Unit of the New York University Hospital.

of motile organisms, there are certain disadvantages to the TPIA test. We have found that it is necessary to remove reagin from the serums prior to testing with the TPIA procedure when antigen preserved with phenol is employed. The antilipidal antibody is absorbed by the addition of the lipid VDRL particles to the serums, separation being effected by centrifugation. Like the TPI test it has the obvious disadvantage of requiring the tedious counting of treponemes with the dark-field microscope. Therefore, it is not suitable for use in large-scale testing.

The TPCF test devised by Portnoy and Magnuson is a procedure which employs as an antigen an aqueous desoxycholate *extract* of the Nichols strain T. pallidum. Since the lipidal component of the treponeme is discarded, this antigen has excellent specificity. The test is a simple complement-fixation procedure based upon the one-fifth volume Kolmer-Wassermann technique. It has the advantage of greater sensitivity than the TPI test in early syphilis as well as speedier execution and, therefore, greater adaptability to mass performance. Nevertheless, as in the TPI and TPIA tests, the production of the antigen requires the harvesting of treponemes from rabbit syphilomas. The resultant expense of this antigen precludes its general use in routine hospital laboratories. For this reason, the development of a specific serologic test for syphilis employing an antigen derived from inexpensively produced cultured treponemes becomes extremely important.

In 1922 Reiter [10-14] infected rabbits with a strain of T. pallidum which was cultivated in an anaerobic fluid medium consisting of diluted horse serum to which boiled liver had been added. Over a period of years this strain lost its virulence, and it was no longer possible to successfully infect rabbits with it, although it could be kept alive in an artificial medium. Later Gaehtgens [15,16] experimented with the strain and produced a useful antigen called Palligen, which was a concentrated suspension of purified Reiter treponemes in carbolized saline. Klopstock [17,18] was the first to obtain positive reactions in the serums of syphilitic patients with a dense alcoholic suspension of this strain. In 1940 Erickson and Eagle [19] investigated the serologic antigenicity of Palligen in a series of 490 syphilitic serums. In this study they obtained a higher degree of sensitivity and specificity with the treponemal antigen than with the routine Wassermann and Eagle lipidal antigens. Eagle and Hogan [20] hypothesized that T. pallidum, as well as cultured spirochetes, contain an antigenic factor (lipidal) which resembles the reactive constituent (lipidal) of tissue extract. Kolmer and his co-workers,[21] employing Palligen in tests with serums of patients with syphilis, leprosy, and malaria, observed a higher incidence of false-positive reactions in the latter two diseases with the Reiter antigen than with the routine lipidal antigens. For this reason the employment of the whole Reiter treponeme in the serodiagnosis of syphilis was discarded in this country.

Since the *whole* Reiter treponeme had been proven to be unsatisfactory as an antigen, D'Alessandro and his co-workers [22-24] have been investigating the antigenicity of various fractions of this micro-organism. Employing absorption experiments with syphilitic serum, they concluded that the Reiter treponeme consisted of four different fractions: two lipid fractions, a thermostabile polysaccharide fraction, and a thermolabile protein fraction. It is the protein fraction obtained by cryolysis which has demonstrated the greatest promise as a satisfactory antigen. Preliminary studies by Cannefax and Garson [25] have demonstrated excellent sensitivity and specificity employing this antigen in a complement-fixation test. Rein, Kelcec, D'Alessandro, and de Bruijn [26] have also investigated the sensitivity and specificity of this soluble thermolabile protein fraction of the Reiter treponeme in a complement-fixation test for syphilis. The antigen

TABLE 1.—*Early Syphilis (Sixty-One Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	83	41	8	10	59
TPCF	89	41	13	7	61
RKCF	84	33	9	8	50
TPIA	80	25	6	8	39
TPI	75	6	0	2	8
STS	71				61

TABLE 2.—*Late and Late Latent Syphilis (Ninety-Five Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	92	59	18	7	84
TPCF	97	74	18	3	95
RKCF	92	47	12	5	64
TPIA	100	47	7	0	54
TPI	88	13	1	2	16
STS	95				95

employed in their study was prepared by de Bruijn,[27] with use of the technique of D'Alessandro. The protein extract Reiter antigen was adapted to a one-fifth-volume Kolmer technique as employed by Portnoy and Magnuson in the TPCF test.

The present study is a comparative evaluation of the Reiter protein complement-fixation (RPCF) test in a group of treated and untreated patients with early syphilis (Table 1), late and late latent syphilis (Table 2), central nervous system syphilis (Table 3), and congenital syphilis (Table 4). In addition, the specificity of the procedure is evaluated in a group of normal patients (Table 5) and a group of non-syphilitc biologic-false-positive reactors (Table 6). Comparison of the sensitivity and specificity of the RPCF with the TPCF is the prime objective of this evaluation, since the techniques of these two procedures are identical, the one-fifth-volume Kolmer-Wassermann technique being employed in each instance. Observations are also recorded with respect to the TPI test, the TPIA test, and the RKCF test. The last procedure is also one employing Reiter protein antigen in a complement-fixation test, but the technique used is a modification of the Kent[28] technique. In some instances critical analysis of the above three tests is not possible because of the relative paucity of serums examined.

TABLE 3.—*Central Nervous System Syphilis (Twenty-One Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	88	15	0	2	17
TPCF	90	17	2	2	21
RKCF	85	15	2	3	20
TPIA	94	13	4	1	18
TPI	80	4	0	1	5
STS	95				21

TABLE 4.—*Congenital Syphilis (Seventeen Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	92	10	1	1	12
TPCF	100	16	1	0	17
RKCF	93	11	2	1	14
TPIA	100	9	1	0	10
TPI	100	2	0	0	2
STS	100				17

Comments and Conclusions

The results of the above study indicate that the RPCF test, employing protein extract of cultured Reiter treponemes as an antigen, *compares favorably* in *sensitivity* with the TPCF test, employing a desoxycholate aqueous extract of the viru-

TABLE 5.—*Normal Seronegative Patients (Forty-One Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	0	0	0	35	35
TPCF	0	0	0	41	41
RKCF	0	0	0	32	32
TPIA	0	0	0	23	23
TPI	0	0	0	4	4
STS	0				41

TABLE 6.—*Biologic-False-Positive Reactors (167 Patients)*

	Reactive, %	Reactive, No.	Weakly Reactive, No.	Non-reactive, No.	Patients, No.
RPCF	0	0	0	153	153
TPCF	0	0	0	167	167
RKCF	0	0	0	95	95
TPIA	0	0	0	95	95
TPI	0	0	0	42	42
STS	100				167

lent Nichols-strain treponeme as an antigen. The *specificity* of the RPCF test in the study outlined is 100%, there being no reactivity with the serums of normal patients and of biologic-false-positive reactors.

This test procedure has the further advantage of inexpensiveness of the antigen as well as simplicity of performance and suitability for mass testing.

The favorable results obtained in this study warrant additional investigation and confirmation.

Department of Dermatology, New York University Post-Graduate Medical School, 550 1st. Ave. (16).

REFERENCES

1. Noguchi, H.: A Method for the Pure Cultivation of Pathogenic Treponema Pallidum (Spirochaeta pallida), J. Exper. Med. 14:99-108, 1911.

2. Noguchi, H.: Über die Gewinnung der Reinkulturen von pathogener Spirochaete pallida und von Spirochaete pertenuis, München med. Wchnschr. 58:1550-1551, 1911.

3. Noguchi, H.: Experimental Research in Syphilis, with Especial Reference to Spirochaeta Pallida (Treponema Pallidum), J. A. M. A. 58: 1163-1172, 1912.

4. Nelson, R. A., Jr.: Factors Affecting the Survival of Treponema Pallidum in Vitro, Am. J. Hyg. 48:120-132, 1948.

5. Nelson, R. A., Jr., and Mayer, M. M.: Immobilization of Treponema Pallidum in Vitro by Antibody Produced in Syphilitic Infection, J. Exper. Med. 89:369-393, 1949.

6. Nelson, R. A., Jr.: The "Adhesion-Disappearance" Phenomenon: A Specific in Vitro Immunologic Reaction Between Treponema Pallidum, Antibody, and Normal Blood Cells, J. Clin. Invest. 32:592, 1953.

7. Nelson, R. A., Jr.: The Immune-Adherence Phenomenon: An Immunologically Specific Reaction Between Microorganisms and Erythrocytes Leading to Enhanced Phagocytosis, Science 118: 733-737, 1953.

8. Rein, C. R., and Kelcec, L. C.: The Treponema Pallidum Immune Adherence Test with a Phenolized Antigen, Am. J. Clin. Path. 28:417-422, 1957.

9. Portnoy, J., and Magnuson, H. J.: Immunologic Studies with Fractions of Virulent Treponema Pallidum: I. Preparation of an Antigen by Desoxycholate Extraction and Its Use in Complement Fixation, J. Immunol. 75:348-355.

10. Reiter, H.: Beitrag zur Frage der Wiederinfektion bei experimenteller Kaninchensyphilis, Zentralbl. Bakt. 92:534-540, 1924.

11. Reiter, H.: Die Reinzüchtung der Spirochæte dentium, Deutsche med. Wchnschr. 51:303-304, 1955.

12. Reiter, H.: Über Fortzüchtung von Reinkulturen der Spirochæte pallida, Spirochæta dentium, und Spirochæte recurrens, Klin. Wchnschr. 5:444-445, 1926.

13. Reiter, H.: Praktische Verwertung der Reinkulturen von Spirochæte dentium und pallida, Dermat. Wchnschr. 83:1199-1201, 1926.

14. Reiter, H.: Spirochätenkulturen und ihre Anwendung, Dermat. Wchnschr. 89:1401-1406, 1929.

15. Gaehtgens, W.: Theoretisches und Praktisches über die Wirkung eines karbolisierten wässerigen Pallida-Antigens, Ztschr. Immunitätsforsch. 63: 398-427, 1929.

16. Gaehtgens, W.: Die bisherigen Erfahrungen mit der Pallidareaktion zum serologischen Luesnachweis, Arch. Dermat. u. Syph. 176:42-62, 1937.

17. Klopstock, F.: Die Entstehung der syphilitischen Blutveränderung und ihr Nachweis mittels alkoholischen Spirochätenextrakts, Deutsche med. Wchnschr. 52:226-229, 1926.

18. Klopstock, F.: Die Entstehung der syphilitischen Blutveränderung und die Eigenschaften eines Spirochätenimmunserums, Deutsche med. Wchnschr. 52:1460-1462, 1926.

19. Erickson, P. T., and Eagle, H.: Evaluation of Spirochete Complement Fixation Reaction in Comparison with the Eagle Flocculation and Wassermann Procedures, Ven. Dis. Inform. 21:31-37, 1940.

20. Eagle, H., and Hogan, R. B.: On the Presence in Syphilitic Serum of Antibodies to Spirochetes, Their Relation to So Called Wassermann Reagin and Their Significance for the Serodiagnosis of Syphilis, J. Exper. Med. 71:215-230, 1940.

21. Kolmer, J. A.; Kast, C. C., and Lynch, E. R.: Studies on the Role of Spirochaeta Pallida in the Wassermann Reaction: Complement Fixation in Syphilis, Leprosy, and Malaria with Spirochetal Antigens, Am. J. Syph., Gonor. & Ven. Dis. 25: 300-318, 1941.

22. D'Alessandro, G.; Oddo, F.; Comes, R., and Dardanoni, L.: Sulla struttura antigene del T. pallidum: Recerche sullo stipite coltivabile di Reiter, Riv. Ist. Sieroterap. ital. 24:134-166, 1949.

23. D'Alessandro, G.; Oddo, F., and Dardanoni, L.: The Antigens of the Cultured Treponema Pallidum (Reiter's Strain) and the Antispirochetal Antibodies in Human Syphilis, J. Ven. Dis. Inform. 31:314-315, 1950.

24. D'Alessandro, G., and Dardanoni, L.: Isolation and Purification of the Protein Antigen of the Reiter Treponeme, Am. J. Syph. 37:137-150, 1953.

25. Cannefax, G. R., and Garson, W.: Reiter Protein Complement Fixation Test for Syphilis, Pub. Health Rep. 72:335-340, 1957.

26. Rein, C. R.; Kelcec, L. C.; D'Alessandro, G., and de Bruijn, J. H.: Sensitivity and Specificity of Reiter Protein Complement Fixation (RPCF) Test for Syphilis, J. Inv. Derm. 28:459-462, 1957.

27. de Bruijn, J. H.: The Application of a Protein Fraction Derived from Treponema Pallidum (Reiter Strain) as an Antigen in the Serodiagnosis of Syphilis, Antonie van Leeuwenhoek 23:201-206, 1957.

28. Kent: Personal communication to the authors.

Larva Currens

A Distinctive Variant of Cutaneous Larva Migrans Due to Strongyloides Stercoralis

ROBERT P. ARTHUR, M.D., and WALTER B. SHELLEY, M.D., Philadelphia

Although our experience with larva migrans is limited by virtue of our geographic position, we recently studied an example with such distinctive features as to merit the special attention of all dermatologists. Indeed, we have ventured to emphasize the clinical distinctiveness of this type of larva migrans by giving it a separate name, larva currens. We feel it merits special categorization since it can be diagnosed purely by its clinical picture, a picture which has led us to name it "racing larva," i. e., larva currens. It is a form known to the parasitologist and tropical physician [1] but one apparently unknown to the dermatologist. We hope that this article will provide an appropriate cross fertilization of knowledge.

Report of a Case

The patient, a white 46-year-old housewife, developed a pruritic erythematous urticarial lesion of the medial aspect of the left midthigh on April 15, 1957. The eruption progressed from time to time in an irregular serpiginous linear fashion. Systemic chloramphenicol (Chloromycetin) and erythromycin therapy for 10 days was without effect. Admitted to the hospital on April 28, she was considered to have a possible cellulitis, lymphangitis, or thrombophlebitis. On the left thigh she presented tender erythematous serpentine cords which showed periodic urticarial extensions. She had marked enlargement of the left inguinal nodes. Her history and general physical examination were noncontributory. Conjoint systemic streptomycin, chloramphenicol, and penicillin therapy, bed rest, and hot compresses were without effect. Her oral temperature ranged between 99.0 and 99.6 F. A blood study on April 29 revealed hemoglobin of 12.9 gm. %, and a white cell count of 15,600 per cubic millimeter, with 73% neutrophils, 22% lymphocytes, and 5% eosinophils. On May 4 the white cell count was 13,900, with 63% neutrophils, 29% lymphocytes, 7% eosinophils, and 1% monocytes. Blood sugar, urea nitrogen, and urinalysis were normal.

We were called in consultation on May 3, at which time the entire left thigh was encircled by a wide, rapidly extending band of urticaria. Figure 1 presents a view of part of this lesion as photographed on May 3. The raised urticarial band, over 5 cm. in width, presented a fine distinct erythematous central linear lesion. This central line extended a short distance ahead of the developing urticaria. It was possible actually to see advancement of the lesion within a matter of 10 minutes. After a period of hours the lesion would cease moving, only to resume movement at an unpredictable time the following day. The urticaria subsided slowly, leaving a distinct brownish track consisting of a brownish, slightly infiltrated line. The patient presented only one track, all of her lesions being traceable as one continuous line.

The patient denied any travel, animal contact, or previous helminthic disease. She had had no previous skin disease. However, she did recall having cleaned unwashed, sand-contaminated celery a short time before the onset of the eruption. A diagnosis of larva migrans was made, and the natural course was observed for 24 hours.

On May 4 and 6 large areas at the advancing end of the lesion were sprayed with ethyl chloride to the point of blister formation, without any effect on the progress of the larva. On May 8 an intradermal injection of crystalline lyophilized trypsin (1 ml. of a concentration of 10^{-3} in isotonic saline solution) was made at the most advanced point of the lesion. This single injection was curvative, since no further extension of the skin lesion developed. At the time of this writing, nine months later, no further difficulty has been experienced. Figure 2 details the course of the larva from Saturday, May 4, through Wednesday, May 8, when it was apparently killed by the proteinase. This photograph was taken May 9 and does not show the clinical characteristics. It simply demonstrates the rapid rate of movement

Submitted for publication Feb. 20, 1958.

From the Department of Dermatology, University of Pennsylvania School of Medicine.

Fig. 1.—View of acute lesion of larva currens on mediolateral upper left thigh. Note broad band of urticaria which tapers down near advancing end of lesion. The end of the lesion here is at the inguinal fold. A portion of the old serpiginous track can be seen to the left of the medial thigh.

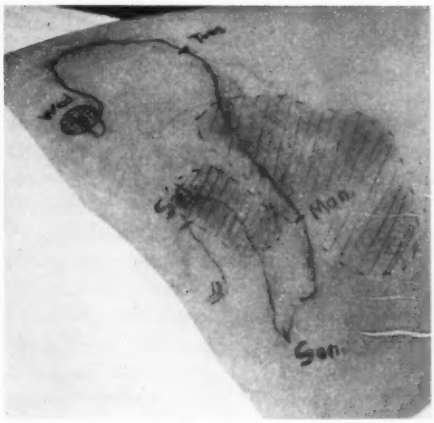


Fig. 2.—The route of the larva is mapped on the left medial thigh. Note the rapid progress of the lesion, the speed of which varied from 7 to 11 cm. in a few hourly spurts per day. The hatched areas are sites of the ineffective ethyl chloride spray. The cross hatched circle is the site at which the larva was stopped by the injection of trypsin intradermally. This photograph was taken after the urticaria had subsided and is not a clinical representation of the lesion.

of the larva (7 to 11 cm. daily during a few hours out of each 24. The hatched areas show the residual erythema of the ethyl chloride-treated sites. The cross hatched circle, labeled "Wednesday," is the site of the proteinase injection. Faint older parts of the linear trail may be seen indistinctly.

The patient has had no further evidence of skin disease or illness of any type during the year ensuing.

Comment

The clinical result with trypsin delighted us, but we continued to puzzle over the strange clinical pattern we had seen. We had seen a "racing larva" move inches in hours, and we had seen a giant urticarial band develop. We had previously seen patients with fine linear slow-moving larva migrans, but here was a different problem. Was this an allergic reaction and one which prodded the parasite to celerity? The standard textbooks of dermatology as well as our past experience afforded us no help.

The library revealed the answer to our clinical query. Creeping eruption in its classical sense encompasses only the progressive linear lesions which develop as a result of the intracutaneous wanderings of the larval, i. e., young, forms of either *roundworms or flies.* In the broad sense one might consider scabies and other burrowing lesions due to acarine parasites (Tetranychus), but practically scabies has always been clinically separated from larva migrans. Thus, we can outline the causes of *creeping eruption* in the Table.[2,3]

Causes of Cutaneous Larva Migrans

I. Migratory Helminthiasis: Nematode (Roundworm) Larvae			
A. Nonhuman Species	Common Name	Incidence	Clinical Distinction
(1) Ancylostoma braziliense	Cat, dog hookworm	Commonest	Thread-like pruritic migratory burrow; may persist for months, moving 1 or 2 cm/day
(2) Ancylostoma caninum	Dog hookworm	Common	Papular, rarely linear lesions; disappear in 2 wk.
(3) Gnathostoma spinigerum	Pig, cat	Rare	Deep burrows, band-like infiltrates, at times furunculoid; may be active for years
(4) Uncinaria stenocephala	European dog hookworm	Rare	Thread-like pruritic migratory burrow; may persist for months, moving 1 or 2 cm/day
(5) Bunostomum phlebotomum	Cattle hookworm	Rare	Papules, migration for few millimeters; clear in 2 wk.
B. Human Species			
(1) Ancylostoma duodenale	Human hookworm	Common	Papulovesicular, pruritic, minimal migration in skin, disappears within 2 wk.
(2) Necator americanus	Human hookworm	Common	Papulovesicular, pruritic, minimal migration in skin, disappears within 2 wk.
(3) Strongyloides stercoralis	Human thread worm	Rare	Urticarial band extending up to 10 cm/day; originates in perianal area; persists for weeks; recurrent for years owing to autoinoculation from intestinal infection
II. Migratory Myiasis: Botfly Larvae			
Species			
1 Gastrophilus intestinalis 2 Gastrophilus hemorrhoidalis 3 Gastrophilus nasalis	Horse botfly	Rare	Typical superficial migrating serpentine lesions
4 Hypoderma bovis 5 Hypoderma lineatus	Cattle warble fly	Rare	Serious deep furunculoid lesions; very slow migration

Dermatologic texts [4] have stressed the fact that most cases are attributable (by assumption) to Ancylostoma braziliense. Distinction of any type rests purely on histologic examination and parasitological identification of the offending larva. To this end the larval morphology has been exquisitely detailed by Nichols recently.[5] We despaired of any precise elucidation of the type of larva migrans in our patient until we read the masterful review article of Beaver.[1] This was published in *Experimental Parasitology,* in 1956, and should be consulted for a comprehensive account of larva migrans.

Beaver made it apparent that we most likely had been observing and treating a case of Strongyloides stercoralis larval infection. It is evident from his review of experimentally produced larva migrans that Strongyloides larvae produce a distinctive clinical pattern that can be diagnostic.

All of the reported clinical cases of creeping eruption proven to be due to S. stercoralis larvae have had the following unique clinical features: (1) involvement of perianal area, due to autoinfection from larvae coming out with the fecal matter; (2) an extraordinary band of urticaria associated with the presence of the larva in the skin; (3) a burrow advancing with almost unbelievable speed, as much as four inches an hour.

In 1926, Fülleborn [6] gave us the first full account of creeping eruption known to be caused by S. stercoralis. He vividly described his own eruption as well as that seen in seven others. He believed that perianal autoinoculation accounted for the clinical picture of radiating linear urticarial lesions over the buttocks, thighs, and lower trunk. All of these patients had long-standing intestinal infections with the adult worm. He further reproduced the disease in himself by the application of a dozen larvae to his lower arm. Within three minutes of penetration he noted a wheal 2.5 cm. in diameter. By two hours the wheal was 8 cm. in size. Linear swellings then progressed outward at great speed, one developing the length of 13 cm. in two and one-half hours. Urticarial swelling reappeared off and on for several months. Experimental production of the skin disease had also been achieved earlier by Brumpt [7] and was later confirmed by Sandground.[8] Fülleborn [9] and others [10] demonstrated that the urticaria may be due to an allergic state, since an antigen prepared from the Strongyloides larva gave positive skin tests in patients with strongyloidiasis but not in normal persons or persons infected with other intestinal parasites. Caplan,[11] Napier,[12] and others [13,14] also have recently described larva migrans due to S. stercoralis. Here, again, the urticaria and speed of movement were noteworthy. Extensions were seen to develop as far as 10 cm. in one hour. Stool cultures were 98% positive for S. stercoralis. Special note should be made of Sandosham's scholarly review,[13] which is an interpretative study of the literature and his own experimental observations.

S. stercoralis is one of the true unsegmented roundworms (Nematoda). It parasitizes the intestinal tract as an adult female worm measuring approximately 2 mm. in length and only 50μ in width. In contrast to hookworms, whose progeny are excreted from the host as ova, S. stercoralis ova may hatch within the mucosa of the small bowel into a noninfective larval stage. A later stage, the tiny filariform larva (0.5μ, 15μ), may develop in the intestine or on fecally contaminated skin. This is then capable of *reinfecting* or infecting by entering the skin. Lewert and Lee [15] have studied this phase carefully. They have shown that the Strongyloides larvae secrete proteinases, collagenase, and other enzymes which permit penetrance of the normal intact epidermis and corium. They then go into the circulation and, via the lungs, back into the gastrointestinal tract. The reinfection accounts for a unique feature of larva currens, viz., its localization and recurrence. Relatively asymptomatic chronic

infections occur with eosinophilia as the solitary clinical feature. Strongyloidiasis is endemic in warm temperature zones and occurs in man. Rarely it is found in dogs and cats. Infection is by contact of the skin or buccal mucosa with the filariform larva from fecal contaminated soil. These infections are rare in the northern United States, but increasing travel alerts one to the possibility of minor epidemics.[16] Fortunately the new anthelmintic, dithiazanine, is effective against strongyloidiasis.[17]

We feel that this distinctive Strongyloides creeping eruption known to the tropical medical literature should be likewise recognized in the dermatological writings. It is our feeling, furthermore, that the patient we are reporting had this condition. Her clinical pattern duplicated that seen in proven cases. Unfortunately, we have not any parasitological proof of this diagnosis, but we have elected to report our findings to point up the clinical syndrome. Any future patients presenting this type of eruption should have extensive stool examinations to demonstrate possible Strongyloides larvae. Moreover, we have proposed a name, larva currens (Latin: racing larva), to indicate the nature and uniqueness of this specific form of larva migrans. An alternate descriptive term, strongyloidiasis cutis, fails to indicate the major clinical feature of rapidity of larva movement.

Our patient had but a single larva in the skin with but a single long continuous tunnel. This permitted us to assess rather accurately the clinical treatment. We assume that the ethyl chloride was ineffective owing to the depth at which the larva was traveling. The establishment of a thermal equilibrium prevents deep freezing with this modality. We employed trypsin because of the known lethal effects of all proteolytic enzymes[18,19,20] on many nematode infections of the intestine. In our case the effect of trypsin was rapid and complete. The larva was apparently killed by a single injection at the advancing end of the burrow. We would assume that this was a primary infection, possibly acquired from soil-contaminated vegetables. The failure to develop further attacks in one year militates against a diagnosis of intestinal strongyloidiasis.

Finally, it is important to comment on the nature of several clinical features in this disease. We feel that the pruritus and urticaria result in part from the proteinase secretion by the larva.[20] In addition, the larva may well eliminate another histamine liberator similar to that isolated from the roundworm.[21] Animal studies suggest that the urticarial response to Strongyloides larvae is unique[15] in the absence of any allergic responses. However, in the patient, as Fülleborn[9] demonstrated, allergy does play a role and explains in part the giant urticaria. Fülleborn's studies[22] must also be cited to suggest that the erratic course of the larva is largely dictated by heat gradients. The larvae all migrate to the warmer points.

Summary

Attention is directed to a distinctive variant of larva migrans due to intracutaneous Strongyloides stercoralis larvae. The literature would indicate that it can be diagnosed on the clinical grounds of perianal topography, unusual urticarial response, and extremely rapid advancement of the burrow. Proven cases have invariably presented evidence of chronic intestinal strongyloidiasis.

A case presenting these clinical characteristics is described in which cure was achieved by the local injection of trypsin.

The name "larva currens" is proposed to point up the distinctiveness of the dermatological patterning of this cutaneous strongyloidiasis.

Duhring Laboratories, Department of Dermatology, University Hospital, University of Pennsylvania (4).

REFERENCES

1. Beaver, P. C.: Larva Migrans, Exper. Parasitol. 5:587, 1956.

2. Mackie, T. T.; Hunter, G. W., III, and Worth, C. B.: A Manual of Tropical Medicine, Ed. 2, Philadelphia, W. B. Saunders Company, 1954.

3. Faust, E. C.: Human Helminthology, Ed. 3, Philadelphia, Lea & Febiger, 1949.

4. Pillsbury, D. M.; Shelley, W. B., and Kligman, A. M.: Dermatology, Philadelphia, W. B. Saunders Company, 1956.

5. Nichols, R. L.: The Etiology of Visceral Larva Migrans: II. Comparative Larval Morphology of Ascaris Lumbricoides, Necator Americanus, Strongyloides Stercoralis and Ancylostoma Caninum, J. Parasitol. 42:363, 1956.

6. Fülleborn, F.: Hautquaddeln und "Autoinfektion" bei Strongyloidesträgern, Arch. Schiffs- u. Tropen-Hyg. 30:821, 1926.

7. Brumpt, E.: Précis de Parasitologie, Ed. 2, Paris, 1922.

8. Sandground, J. H.: Some Studies on the Susceptibility, Resistance, and Acquired Immunity to Infection with Strongyloides Stercoralis (Nematoda) in Dogs and Cats, Am. J. Hyg. 8:507, 1928.

9. Fülleborn, F.: Spezifische Kutanreaktionen bei Infektion mit Strongyloides und anderen Helminthen, Arch. Schiffs- u. Tropen-Hyg. 30:732, 1926.

10. Brannon, M. J. C., and Faust, E. C.: Preparation and Testing of a Specific Antigen for Diagnosis of Human Strongyloidiasis, Am. J. Trop. Med., 29:229, 1949.

11. Caplan, J. P.: Creeping Eruption and Intestinal Strongyloidiasis, Brit. M. J. 1:396, 1949.

12. Napier, L. E.: Strongyloides Stercoralis Infection: Strongyloidiasis Among Ex-Prisoners-of-War, J. Trop. Med. 52:46, 1949.

13. Sandosham, A. A.: An Investigation into the Association of Creeping Eruption with Strongyloides Infection Contracted in the Far East, J. Helminthol. 26:1, 1952.

14. Galliard, H., and Chabaud, A. G.: Anomalies, s'éteignant par passage chez le chien, d'une souche de Strongyloides stercoralis, isolée d'un cas d'urticaire migrant, Ann. Parasitol. 27:588, 1952.

15. Lewert, R. M., and Lee, C.: Studies on the Passage of Helminth Larvae Through Host Tissues, J. Infect. Dis. 95:13, 1954.

16. Birch, C. L., and Anast, B. P.: The Changing Distribution of Helminthic Diseases in the United States, J. A. M. A. 164:121, 1957.

17. Swartzwelder, J. C., et al.: Dithiazanine, An Effective Broad-Spectrum Anthelmintic, J. A. M. A. 165:2063, 1957.

18. Weise, H.: Über die Wurmbekämpfung durch Enzyme, Med. Klin. 45:1096, 1950.

19. Hwang, K., and Ivy, A. C.: A Review of the Literature of the Potential Therapeutic Significance of Papain, Ann. New York Acad. Sc. 54:161, 1951.

20. Shelley, W. B., and Arthur, R. P.: Studies on Cowhage (Mucuna Pruriens) and Its Pruritogenic Proteinase, Mucunain, A. M. A. Arch. Dermat. 72:399, 1955.

21. Uvnäs, B.: The Mechanism of Histamine Liberation, J. Pharm. & Pharmacol. 10:1, 1958.

22. Fülleborn, F.: On the Larval Migration of Some Parasitic Nematodes in the Body of the Host and Its Biological Significance, J. Helminthol. 7: 15, 1929.

Observations on the Role of Vehicles in Percutaneous Penetration

J. B. SHELMIRE Jr., M.D., Dallas, Texas

A previous study in this series [1] examined the relation between the vehicle and the relative rate of diffusion to the skin surface of an incorporated substance.

The present investigation concerns the effect of the vehicle on the percutaneous penetration of substances known to penetrate human skin.

The Vehicles

Vehicles were previously classified as (1) oil-in-water emulsion, (2) aqueous, (3) water-in-oil emulsion, (4) grease, and (5) nonvolatile water-miscible.

An example of each type was used in this study, with the exception of an aqueous vehicle. Rapid evaporation and subsequent concentration of incorporated substances make an aqueous vehicle unsuitable for this study. An anhydrous water-in-oil emulsion was included for the investigation of several specific points.

The oil-in-water emulsions were compounded to meet the requirements thought necessary for a series of test vehicles. Two are included, since all of the drugs studied were not compatible with any one. The nonionic, 2(*a*), was preferred when possible, since it minimizes any alteration of results due to detergent injury of the skin. Both vehicles are of a type designed to inhibit evaporation of the aqueous phase and maintain as much as possible their original form over the test period.[2] An oxycholesterol-petrolatum ointment base (Aquaphor) was arbitrarily chosen as the water-in-oil emulsion; however, results were found to be similar with use of hydrous wool fat (lanolin) or a sorbitan sesquioleate preparation.

The test vehicles were all of approximately equal viscosity at room temperature, although they were unequal upon elevation to skin temperature. The phase-volume ratios (proportion of oil to water) of the hydrous emulsion bases were also made exactly equal.

The following vehicles were used.

1. Polyethylene glycol (Carbowax 1500)
2. (*a*) Ceresin, 8.0 gm.
   Cetyl alcohol, 2.6 gm.
   Sorbitan monostearate polyoxyalkylene derivative (Tween 60), 8.0 gm.
   Glyceryl monostearate, 2.8 gm.
   Petrolatum, 58.0 gm.
   Water, 30.0 gm.
   (*b*) Cetyl alcohol, 2.6 gm.
   Glyceryl monostearate, 9.0 gm.
   Sodium lauryl sulfate, 1.8 gm.
   Heavy liquid petrolatum, 33.5 gm.
   Petrolatum, 33.5 gm.
   Water, 30.0 gm.
3. Aquaphor, 80.4 gm.
   Water, 30.0 gm.
4. Aquaphor
5. Petrolatum

Substances Incorporated

The drugs chosen for this study all produce a localized effect on the skin, primarily a vascular change at the minimal concentrations used. Several of the irritants are also capable of producing epidermal changes; however, these clearly followed the vascular changes, which were used as the criteria of penetration.

The irritants used included mercury bichloride, which is soluble in water; croton oil, which is soluble in petrolatum and dispersible in Carbowax 1500, and salicylic

Submitted for publication Jan. 22, 1958.

Clinical Instructor in Dermatology, Southwestern Medical School of The University of Texas.

acid, which is only slightly soluble in water, although soluble in Carbowax 1500.

The nonirritants studied included ephedrine alkaloid, which is very soluble in both water and petrolatum, and hydrocortisone alcohol, which is almost completely insoluble in both.

Method of Application

A single subject was used throughout the study, and the site of application was in all instances the flexor surface of the forearm. The vehicles, all containing the specified concentration of the drug under consideration, were applied simultaneously to closely grouped areas, each about 1.5 cm. in diameter. A reasonable proximity of the test areas was found necessary to minimize errors due to change in skin thickness, especially when threshold concentrations were used. A film of ointment 2 to 3 mm. thick was applied, since early results with very thin manually applied films were too variable. Above a certain minimum, small errors in thickness do not appear to affect the results, which were consistent and easily reproducible.

With the exception of hydrocortisone alcohol, where the clinically accepted concentration of 1% was used, a threshold concentration of each drug was experimentally determined. This was done by gradually increasing the concentration in all vehicles simultaneously until a definite reaction was obtained with one or more of the vehicles after a three-hour period of application. These concentrations proved to be 1.5% for mercury bichloride, 2.5% for salicylic acid, 5% for croton oil, and 2% for ephedrine alkaloid. All drugs in the above concentrations were compatible with emulsion 2(*a*) except salicylic acid, which was incorporated in the alternate emulsion 2(*b*).

The standard period of application was three hours, with the vehicles left uncovered. At the end of this period all vehicles were removed with soap and water, and the results were noted.

Results

Croton Oil.—The reaction produced by croton oil consisted of an erythema beginning three to four hours after removal of the vehicles and reaching a peak at about seven hours after removal. Petrolatum produced the most intense reaction; the erythema, however, appeared to spare the follicular areas. The hydrous water-in-oil emulsion produced a less-intense reaction consisting of erythematous papules of entirely follicular distribution. No reaction was noted with the remaining vehicles.

In order to evaluate the role of hydration of the skin due to sweat accumulation at the skin-vehicle interface, an area was pretreated by application of a gauze pad saturated with isotonic saline for one and one-half hours. The area was allowed to dry in air, and croton oil in petrolatum was applied simultaneously to both the pretreated area and an adjacent control area. A marked acceleration and accentuation of response were noted in the pretreated area.

Salicylic Acid.—Both of the water-containing emulsions produced a diffuse erythema, beginning shortly after removal of the vehicles and lasting six to seven hours. The reaction appeared to be slightly more intense with the oil-in-water emulsion. No reaction was noted with the anhydrous water-in-oil emulsion, petrolatum, or Carbowax 1500.

Mercury Bichloride.—The most intense reaction obtained was with the oil-in-water emulsion and consisted of a diffuse erythema beginning about 12 hours after removal of the vehicles and reaching full intensity at 24 hours. A less-intense reaction was noted with the hydrous water-in-oil emulsion and consisted of scattered erythematous papules of follicular distribution.

An incidental finding was that 5% resorcinol, another water-soluble drug, gave an entirely similar pattern of penetration, although the reaction was much quicker to appear. It is compatible with vehicle 2(*b*), although it tends to break the emulsion on prolonged standing.

Ephedrine Alkaloid.—This drug gave an intense reaction in all vehicles except Carbowax 1500. The response, which was at full intensity at the time of removal of the vehicles, consisted of vasodilation and cutis anserina. The reaction subsided in two to three hours.

Another incidental finding was that 2% epinephrine alkaloid gave no response in any of the vehicles. No effort was made to increase the concentration to a threshold level.

Hydrocortisone Alcohol.—Since this drug produces no directly observable effect on the skin surface, an effort was made to evaluate its penetration on the basis of inhibition of various stimuli applied after removal of the vehicles. The stimuli were delivered both immediately upon removal of the vehicles and at time intervals up to three hours after removal. The stimuli included an erythema dose of ultraviolet light,[3] epidermal stripping, and various intensities of solid carbon dioxide application. No consistent inhibition of any of these stimuli was noted on intact skin.

However, with use of the technique of Wells,[4] where the ointment is applied immediately after the surface is stripped, a comparison could be made. The entire test area was stripped with pressure-sensitive tape, and the vehicles were applied for three hours. At the time of removal, complete inhibition of the stripping erythema was noted with all vehicles except Carbowax 1500. The inhibition persisted for about four hours, after which the erythema gradually returned until it was equal to that of adjacent control areas.

Comments on Results

The differences that exist in penetration from individual vehicles over a three-hour period are directly referable to the solubility characteristics of the incorporated drugs. An attempt to explain the results of this study will be made on the basis of the two main functions of a vehicle. The first function is hydration of the skin surface; this appears to promote penetration in some degree, regardless of drug solubility. This is dependent on the secretion of sweat beneath an anhydrous vehicle and may be augmented by water already present in hydrous vehicles. This hydration effect appears to increase as the vehicle becomes more occlusive. The second function of a vehicle is diffusion of the drug to the skin-vehicle interface in adequate concentration; this depends primarily on the degree of solubility of the drug in the vehicle.

Croton oil penetrates most effectively from petrolatum, the most occlusive vehicle in which it is soluble. It is soluble in the external phase of the absorption bases, but occlusion and subsequent hydration are insufficient to give a reaction comparable to that of petrolatum.

It was previously found that several liposoluble substances diffused rapidly to the skin surface when incorporated in Carbowax 1500. This vehicle apparently does not produce the occlusive hydration necessary for the penetration of croton oil. Although initial diffusion may be rapid, this would decrease as the portion of the vehicle at the skin surface dissolved in sweat, with subsequent precipitation of the liposoluble solute.

Salicylic acid penetrates from both of the hydrous emulsion bases, although in a previous study the water-in-oil emulsion alone gave a reaction. The oil-in-water emulsion formulated for this study is considerably more occlusive than the one previously used. The amount of water in the vehicle itself appears to be of importance and would suggest that salicylic acid is absorbed from a saturated solution. However, since salicylic acid is not highly soluble in either phase of the hydrous emulsion bases, phase inversion does not produce the marked difference that occurs when a drug is used that is completely soluble in only one of the phases.

Mercury bichloride is entirely soluble in the aqueous phase of the hydrous emulsion bases; hence, penetration is greatest from the vehicle in which water is the continuous phase and in direct contact with the skin. The primary function of the vehicle in this instance is probably in maintaining solution of the drug over a prolonged period, since rather rapid penetration of water-soluble substances has been demonstrated from water alone.[5,6]

The poor penetration of ephedrine alkaloid from Carbowax 1500 is not surprising, in view of the physical characteristics of this vehicle. Equal penetration from the

remaining vehicles would indicate that it is rapidly absorbed from either an aqueous or an oily medium and is less dependent on prior hydration of the skin.

The penetration of hydrocortisone alcohol through stripped skin at an arbitrary concentration cannot be directly compared with the penetration of any other drug through intact skin at a threshold concentration. In addition to obvious quantitative differences in penetration between stripped and intact skin, the presence of an intact horny layer might produce greater qualitative differences in rates of penetration from various vehicles. This awaits investigation with a more sensitive method.

In either case, the presence of water in the vehicle is probably of little importance, since hydrocortisone alcohol is practically insoluble.

The definite patterns produced on the skin surface by the irritants may be of some significance in understanding routes of penetration. The early sparing of the follicular areas by croton oil in petrolatum might be explained by the higher surface tension of this vehicle in regard to sweat. Sweat would accumulate first about the pore and in the skin sulci, only later displacing petrolatum from the follicles. The maximum reactions with other drug-vehicle combinations were diffuse over the entire test area, although reactions less than the maximum (croton oil and mercury bichloride in the hydrous water-in-oil emulsion) appeared to be predominately follicular. It was also an impression that a decrease in time or concentration gave a reaction more limited to the follicular areas. If correct, this would further confirm the belief that drugs penetrate the skin most easily via the follicular route.[7] The foregoing factors should be considered in the attempt to establish preferential routes of penetration for any particular substance.

Summary of General Factors Affecting Penetration from Vehicles

Hydration of the Skin.—There appear to be two principal ways in which this factor may affect penetration from vehicles: (1) by an effect on the skin itself, making it more permeable, and (2) by maintaining solution at the skin-vehicle interface of those drugs absorbed from an aqueous medium.

The state of hydration of the skin and skin-vehicle interface represents a balance between sweat secretion, evaporation, and the amount of water originally incorporated into the vehicle.

Delivery Rate to the Skin Surface.—The most important factors affecting delivery rate are as follows. The first factor is the solubility of the drug in the vehicle or its external phase. Diffusion to the skin surface is more rapid when the drug is in the molecular state.

The second factor affecting delivery rate is the concentration of the drug. The rate of penetration appears to increase in direct proportion to the concentration, provided the solubility limit of the drug in the particular vehicle is not exceeded. Strakosch and Clark[8] found little increase in the total penetration of poorly soluble sulfonamides with increasing concentration. Shelley and Melton found that the penetration of histamine from aqueous solution increased in proportion to the concentration. These differences may be explained on the basis of solubility.

The third factor is the time of application of the vehicle. This appears to be proportional to total penetration, as long as a concentration gradient exists between the vehicle and the skin. Changes in both degree of hydration of the skin and water content of the vehicle may occur as the time of application is extended. These may produce secondary changes of drug concentration or drug solubility in the vehicle. Widely varying times of application account for many apparent discrepancies between vehicle studies. The lack of difference between hydrous and anhydrous emulsions reported by Polano[9] is understandable in view of his particular method and longer time of application.

Summary

Observations are reported on the effect of a standardized series of vehicles on the penetration of intact human skin by croton oil, salicylic acid, mercury bichloride, and ephedrine alkaloid.

The effect of this series of vehicles on the penetration of hydrocortisone alcohol through stripped skin is also reported.

Hydration of the skin, state of solution of the drug, concentration, and time are discussed as the major factors affecting the total penetration from vehicles.

1410 Medical Arts Building (1).

REFERENCES

1. Shelmire, J. B., Jr.: Factors Affecting the Diffusion of Drugs from Vehicles to the Skin Surface, J. Invest. Dermat. 27:383, 1956.

2. Shelmire, J. B., Jr.: The Influence of Oil-in-Water Emulsions on the Hydration of Keratin, J. Invest. Dermat. 26:105, 1956.

3. Scott, A., and Kalz, F.: The Effect of the Topical Application of Corticotrophin, Hydrocortisone, and Fluorocortisone on the Process of Cutaneous Inflammation, J. Invest. Dermat. 26 361, 1956.

4. Wells, G. C.: The Effect of Hydrocortisone on Standardized Skin-Surface Trauma, Brit. J. Dermat. 69:11, 1957.

5. Shelley, W. B., and Melton, F. M.: Factors Accelerating the Penetration of Histamine Through Normal Intact Human Skin, J. Invest. Dermat. 13:61, 1949.

6. MacKee, G. M.; Sulzberger, M. B.; Herrmann, F., and Baer, R. L.: Histologic Studies on Percutaneous Penetration with Special Reference to the Effect of Vehicles, J. Invest. Dermat. 6:43, 1945.

7. Rothman, S.: The Principles of Percutaneous Absorption, J. Lab. & Clin. Med. 28:1305, 1943.

8. Strakosch, E. A., and Clark, W. G.: Studies on the Penetration of Sulfonamides into the Skin, Am. J. M. Sc. 205:518, 1943.

9. Polano, M. K.: Skin Therapeutics, Amsterdam, Elsevier Press, Inc., 1952.

A Survey of Lupus Erythematosus in the University of Michigan Hospital Since 1948

ESPEY F. CANNON, M.D., Redlands, Calif., and ARTHUR C. CURTIS, M.D., Ann Arbor, Mich.

With the discovery of the lupus-erythematosus-cell phenomenon in 1948 by Hargraves et al.,[1] the study of lupus erythematosus (hereafter L. E.) gained tremendous impetus. Not only was the diagnosis of this most interesting disease greatly facilitated; a much broader concept of it was formulated, based partly on some previous ideas concerning its protean nature[2-5] as well as an improvement in modern methods of study. The allusion to methods of study applies not only to those done in the laboratory but to the clinical and historical approach as well. Whereas until fairly recently most of our general knowledge about L. E. was derived from records, with their inherent deficiencies, the best work in that particular field is now being done by studies of the natural history of the disease as it unfolds under direct observation.[6-9] This latter method compensates very well for the more or less obvious deficiencies in the study of old or closed records. These deficiencies are enhanced by the passage of time. What may have been considered a static fact about the disease a few years ago may not now be necessarily so. This applies particularly to data concerning diagnosis, treatment, awareness of the varied nature of the disease, and prognosis.

The desire and need for an adequate classification of L. E. are still paramount and are largely based on the establishment of the fact that all forms of L. E. are simply varied manifestations of the same disease.[10] For example, a diagnosis of discoid L. E., with no further implications or qualifications, is today entirely unacceptable. And yet, a study of records alone in this disease perforce limits one to the more or less rigid classification on which the diagnosis was originally based. Without adequate appreciation of the many clinical and laboratory variations possible in the disease at almost any stage, and a search for the evidences of systemic abnormality, the preparation of such records renders them valueless for the sake of a complete appraisal of the disease. Of course, these inadequacies are to some extent excusable in records prepared up until the past five years or so. But they vitiate a good study of L. E., and their presence in a study of modern records is frustrating, to say the least. Without regular periodic evaluation of a patient, according to a board concept of L. E., it is impossible to become fully aware of the subtleties of the disease.[6,7,11]

A total of 370 case records of L. E. from the University Hospital, University of Michigan, were studied in this project. Of this number, 126 cases were studied to determine, if possible, how many cases of so-called "discoid L. E." were later found to have made the transition to systematized L. E. It soon became apparent that the investigator was completely at the mercy of the original historian from the standpoint of early time relationships and subsequent happenings. This situation was further amplified by the fact that many different clinical philosophies were em-

Submitted for publication March 14, 1958.

From the Department of Dermatology and Syphilology, University of Michigan Medical School (Arthur C. Curtis, M.D., Professor and Chairman), and the University Hospital, University of Michigan. Formerly Clinical Instructor, Department of Dermatology and Syphilology, University of Michigan Medical School; now associated with The Beaver Medical Clinic (Dr. Cannon).

bodied in the case studies—dermatology, internal medicine, pediatrics, arthritis unit, and, of course, every other hospital service which sought dermatological consultation for its patients presenting cutaneous abnormalities. An occasional case was found in which there was a possible "transition," but there was little if any evidence to show when such a transition had taken place. These data were also sought in the balance of the 370 cases studied thereafter from another standpoint, and a total of 5 which might fulfill the arbitrary criteria was found. Montgomery[2] reports one-third of a series of 30 cases of systematized L. E. as having begun as "discoid L. E." The wide discrepancy in these two sets of figures is found in a comparison with other reports.[12] It is suggested that the small percentage of cases showing this change in University Hospital records may be to a large extent based on the multiple sources of records with their inherent deficiencies. Accordingly, the conclusive validity of observations on these records is open to grave doubt. Who is to say that any given instance of discoid L. E. was not systematized from its very onset, unless appropriate studies lend confirmatory evidence?

Another approach to the University Hospital records was made in the interest of incriminating certain drugs as causative factors in the pathogenesis of L. E. The same 370 records were reviewed, from Jan. 1, 1948, to the time of the study. Again historical inadequacies became grossly apparent. Five cases giving a definite history of the ingestion of "sulfa drugs" during the weeks preceding onset of L. E. were discovered. The intervals varied from a few days up to 26 months of intermittent usage. One patient had taken thiouracil for two months before the onset, and one developed discoid L. E. in the site of a red tattoo (cinnabar). One of those taking sulfonamide had had multiple prophylactic inoculations 10 days before the appearance of her eruption. Four of these cases were diagnosed as systematized L. E.; three, as subacute disseminated L. E. Because of the extremely variable clinical patterns in systematized L. E. it must be realized that these patients are almost all treated with a great variety of drugs, even before the disease becomes apparent on the clinical horizon. For example, a supposedly simple but obscure fever with no other manifestations except for malaise may well be treated with sulfonamides, antibiotics, or acetylsalicylic acid (aspirin) in the interest of "doing something" for the patient before a diagnosis is made. The University Hospital records are replete with references of this nature, and one may safely surmise that potentially sensitizing drugs were used in spite of the fact that in most instances they are not specifically named. This seems particularly true when the vulnerability to infections of patients with L. E. is recalled.[10,12] Furthermore, the literature is filled with allusions to the role of drugs in the pathogenesis of L. E. So, in spite of the statistical inadequacy of the figures derived from this study concerning drugs, it must be realized that drugs with a high index of potential sensitizing ability should be used with caution and respect in treating L. E.[10,12]

The years between July 1, 1934, when the present University Hospital record system was installed, and July 1, 1956, were divided into certain arbitrary eras to determine the relative incidence of L. E. in each and to correlate these figures with different types of therapy in vogue at that time and with the discovery of the L. E. cell. The first era, of two and one-half years, was the so-called presulfonamide period. During this time the relative incidence of L. E. was 0.02% of the total number of out-patient and in-patient registrations at University Hospital. The next era, of six years, has been arbitrarily designated as the sulfonamide era, and during this time the percentage of cases of L. E. rose to 0.08% of the total. Penicillin appeared on the scene in the next era, 1943 through 1947, and the use of sulfonamides

became relatively less frequent. During this period, of five years, 0.12% of all University Hospital cases were diagnosed as L. E. In the final period, 1948 to the end of University Hospital fiscal year 1955-1956, the L. E.-cell test became available and with it the expectation of detecting with certainty a greater number of patients with L. E. who might conceivably have been misdiagnosed previously. However, as far as University Hospital records are concerned, there has been essentially no change in the frequency of diagnosis of L. E. The figure for this period is 0.10% of all cases registered at University Hospital during the last era, representing an insignificant difference as compared with 0.12%, of the previous period. It is of interest to note that in the University Hospital coding system the diagnoses of L. E. and "angiomyositis" were carried under the identical code number until July 1, 1956, when a new classification of disease was inaugurated. Also, cases bearing the diagnosis of "questionable L. E." have been arbitrarily coded as L. E. About 10% of the records delivered for study bore these designations and were, of course, discarded. What percentage of the total of coded cases of L. E. prior to 1948 would fall into these two categories is a matter of speculation, but it might be large enough to affect the figure of 0.12% incidence between 1943 and 1948.

In view of the aforementioned figures, it is thus impossible to say whether or not the incidence of L. E. or the ease of its diagnosis have increased in the population of the University Hospital during recent years. These questions have been of considerable interest elsewhere, however.[7,9] Dubois and others feel that the apparent increase in frequency of systematized L. E. is due to a greater awareness of the disease and the acceptance of the concept that it has a broad clinical spectrum of manifestations, rather than that the actual incidence of the disease is increasing. The development of the L. E.-cell test has increased the frequency of positive diagnosis, and with increasing sensitivity of the test by new techniques and combinations of techniques still more cases of L. E. are being diagnosed.[6,7,11] A great many cases that are now diagnosed readily as systematized L. E. would, in years past, have been classified as rheumatoid arthritis, rheumatic fever, chronic nephritis, Raynaud's disease, or idiopathic pericarditis, to name some of the conditions whose major features might mimic the changes produced by systematized L. E. To further emphasize the broad concept of L. E. and to illuminate the difficulties in determining the true incidence of the disease, there is evidence to show that about a third of all persons who exhibit a persistent so-called biologic false-positive reaction to routine serologic tests for syphilis will at some time develop frank systematized L. E. or episodic forms of chronic illness which conform to those known to occur in systematized L. E.[3,9]

The foregoing also emphasizes the extreme difficulty of applying a rigid classification to L. E., an observation that is amply confirmed by almost all authors on the subject. Reiches has recently[13] suggested the term "lupus erythematosus syndrome," with the simple qualifications of "discoid" and "systematized" phases, depending upon the findings in eacn instance. This classification would appear to be flexible enough, provided a diagnosis of "discoid L. E." were made only after appropriate steps had been taken to rule out systematized L. E. If one accepts Dubois' criteria for manifestations of systemic disease, then 96% of persons with either localized or generalized discoid lesions reveal evidence of systematization by history and physical and laboratory examination. The signs and symptoms investigated in these patients include evaluation of the skin lesions, photosensitivity, arthritis, weight loss, pleurisy, alopecia, fever, Raynaud's phenomenon, nausea, abdominal pain, vomiting, pericarditis, mucous membrane lesions, adenopathy, heart murmurs,

diarrhea, myocarditis, hepatomegaly, pleural effusion, ascites, fundus lesions, convulsions, psychoses, central nervous system damage, and splenomegaly. Laboratory investigations include evaluation of anemia, leukopenia, sedimentation rate, the L. E.-cell phenomenon, serological tests for syphilis, serum proteins, liver function, urinalysis, E. C. G. and skin biopsy. Inasmuch as he is probably the only author who has studied chronic "discoid lupus erythematosus" with his stated objectives, there is little reason at present to doubt the validity of his observations. In one way or another, many authors agree with him in principle but have no actual figures as he does to support their belief. Thus, it can be seen that attempts to formulate arbitrary prognoses for cases of apparent simple chronic "discoid L. E." are foredoomed to failure, and little good can be achieved by trying to find out how many such cases develop frank systematized L. E. Any prognosis should be guarded, and based only on a thorough medical evaluation of the particular case at hand.

In summary, the pitfalls and inherent difficulties in a study of records of cases of L. E. have been shown on a limited basis by this study of 370 cases, and others freely admit the limitations of such efforts.[6-10] There were really no profitable statistical data derived from the study. How then can L. E. be profitably studied with the hope of clearing up the many problems that accompany its management? The need for a comprehensive study of the individual case has already been mentioned. More detailed studies of large numbers of cases should be carried on at the medical center level by properly trained and interested persons. However, these studies should be dynamic and forward looking, embodying the idea that the natural history of L. E. is best learned by watching it unfold from its inception to its conclusion. Only by such work will we ultimately be able to arrive at conclusions concerning its pathogenesis, incidence, clinical vagaries, and prognosis. Only by preconceived and systematized study profiles will we be able to eliminate the inherent uncertainties of the records which have been disclosed by this survey, and, by inference, are reflected in the results of similar surveys done elsewhere and at other times.

2 W. Fern Ave.

REFERENCES

1. Hargraves, M. M.; Richmond, H., and Morton, R.: Presentation of 2 Bone Marrow Elements: The "Tart" Cell and the "L. E." Cell, Proc. Staff Meet. Mayo Clin. 23:25, 1948.

2. Montgomery, H.: Pathology of Lupus Erythematosus, J. Invest. Dermat. 2:343, 1939.

3. Montgomery, H., and McCreight, W. G.: Disseminate Lupus Erythematosus, Arch. Dermat. & Syph. 60:356, 1949.

4. Klemperer, P.: The Pathogenesis of Lupus Erythematosus and Allied Conditions, Ann. Int. Med. 28:1, 1948.

5. Klemperer, P.: Progress in Fundamental Medicine, in The Pathology of Systemic Lupus Erythematosus, edited by J. F. A. McManus, Philadelphia, Lea & Febiger, 1952, pp. 51-69.

6. Dubois, E. L.: Systemic Lupus Erythematosus: Recent Advances in Its Diagnosis and Treatment, Ann. Int. Med. 45:163, 1956.

7. Dubois, E. L., and Martel, S.: Discoid Lupus Erythematosus: An Analysis of Its Systemic Manifestations, Ann. Int. Med. 44:482, 1956.

8. Merrell, M., and Shulman, L. D.: Determination of Prognosis in Chronic Disease, Illustrated by Systemic Lupus Erythematosus, J. Chron. Dis. 1:12, 1955.

9. Moore, J. E., and Lutz, W. B.: The Natural History of Systemic Lupus Erythematosus: An Approach to Its Study Through Chronic Biologic False Positive Reactors, J. Chron. Dis. 1:297, 1955.

10. Haserick, J. R.: Modern Concepts of Systemic Lupus Erythematosus: A Review of 126 Cases, J. Chron. Dis. 1:317, 1955.

11. Harvey, A. M.; Shulman, L. E.; Tumulty, P. A.; Conley, C. L., and Schoenrich, E. M.: Systemic Lupus Erythematosus: Review of the Literature and Clinical Analysis of 138 Cases, Medicine 33:291, 1954.

12. Tumulty, P. A.: The Clinical Course of Systemic Lupus Erythematosus, J. A. M. A. 156: 947, 1954.

13. Reiches, A. J.: The Lupus Erythematosus Syndrome: The Relationship of Discoid (Cutaneous) Lupus Erythematosus to Systemic (Disseminated) Lupus Erythematosus, Ann. Int. Med. 46:678, 1957.

Treatment of Psoriasis with Folic Acid Antagonists

WALTER F. EDMUNDSON, M.D., and WILLIAM B. GUY, M.D., Pittsburgh

Since the reporting of clinical improvement observed in the treatment of psoriasis with aminopterin,[1] our interest has been aroused to reevaluate the results obtained with this drug as well as with its close relative amethopterin. These drugs were used in our private practice in relatively low but therapeutic dosage.

These folic acid antagonists are known [2] to inhibit proliferation of connective tissue, anomalous and undifferentiated cells, and epithelial cells. By successfully competing with their analogue, folic acid, they interfere with the conversion of folic acid to the citrovorum factor which is important in the biosynthesis of nucleic acid components necessary in the development of epithelial cells.

It has been shown that histologic response [2] to aminopterin therapy of psoriatic lesions consists of reduced hyperkeratosis, parakeratosis, and acanthosis which parallel the observed clinical improvement in the psoriatic lesions.

The very nature of the action of aminopterin,* as well as amethopterin,† limits its usage because of its general toxic effect and the possible effects on embryonic tissue in females of the childbearing age. Toxic bone marrow depression, hemorrhage, gastrointestinal ulcerations and bleeding, buccal ulcerations, diarrhea, alopecia, and skin sensitivity reactions have all been observed in persons under treatment with these agents, especially for leukemias of childhood.[3] Leukopenia, thrombopenia, and anemia, as well as increased susceptibility to infections, are manifestations of bone marrow toxic depressions. Possible embryopathic effects on the fetus make the use of this drug in women of childbearing age a matter of concern. It is questionable in many cases whether this type of drug should be prescribed during this period; in any case, considerable caution should be taken.

Submitted for publication March 4, 1958.

* Aminopterin sodium (folic acid antagonist, Lederle): sodium 4-amino-pteroylglutamic acid.

† Amethopterin (Methotrexate, Lederle): 4-amino-10-methylpteroylglutamic acid.

Method

In our series mild toxic effects were rarely observed; no serious untoward reactions were encountered. This was probably due to the limitation of dosage of aminopterin to 0.5 mg. daily for six days, withdrawal for three days, and 0.5 mg. daily for six days, for a total of 6 mg. in 12 doses. When amethopterin (Methotrexate) was prescribed, it was given in the same manner in a dosage of 2.5 mg. for a total dosage of 30 mg. in 12 doses. A course consisted of 12 doses given as above. Some patients were given additional treatment consisting of 0.5 mg. of aminopterin, or 2.5 mg. of amethopterin, daily for nine days, administered three weeks after the original course. Repetition of a course of 12 doses was not prescribed until three or more months had elapsed after the original therapy. The rest periods probably reduced accumulative toxic effects of the drugs. We found that the therapeutic effects obtained in this series occurred in the absence of demonstrable toxic effects. In the treatment of leukemia, toxic and therapeutic effects bear a direct relationship. It is possible that better results might have been obtained with higher, and more toxic, dosage schedules, but we felt that induced toxicity by treatment of this harmless though disagreeable disease was not warranted.

Clinical Material

Thirty-two patients with unequivocal psoriasis of a moderate to severe degree were treated with aminopterin in courses of 6 mg. An additional 4.5 mg. course was given three weeks later in eight of these cases.

Six cases were treated with one or more additional courses of 6 mg. of aminopterin three or more months apart; eighteen were given one course

only. The duration of the disease process varied from 1 month to more than 40 years, 8 having had recognizable psoriasis for less than 1 year, 7, from 1 to 10 years, and 17, for more than 10 years. In age these patients ranged from 17 to 65 years. The group consisted of 16 males and 16 females.

An attempt was made to classify the types of psoriasis observed in these 32 patients. Fourteen had the plaque type; seventeen, a combination of guttate and plaque type, and one had the guttate type. Three had pustular lesions of the palms and soles in addition to other psoriatic lesions.

A series of 17 cases was treated with amethopterin in the same manner as the aminopterin group, with use of 2.5 mg. per dose, a total of 30 mg. in a course. Four patients had an additional 22.5 mg. three weeks after the original course. One was treated with one or more additional 30 mg. courses three or more months after the original course; twelve were treated with one course only. The duration of the disease process varied from 1 month to more than 20 years, six having had psoriasis for less than 1 year, two from 1 to 5 years, four from 5 to 10 years, and five for more than 10 years. In age these patients ranged from 22 years to 74 years. There were 13 women and 4 men.

In this group five were classified as having had guttate psoriasis; three, the plaque type, and nine, a combination of guttate and plaque type.

An additional 13 cases received aminopterin as their original course and amethopterin as their subsequent course or courses.

Twenty-nine, or 47%, of the total of sixty-two cases treated with the folic acid antagonists had only one course of either drug; fifty-four, or 87%, had two or fewer courses of either or both drugs, and eight, or 13%, had more than two courses of treatment.

Results

Results of treatment with either one or both of these drugs proved difficult to express, though in most cases definite improvement was noted. The treatment results were expressed as poor when less than 50% improvement in the lesions was observed, good when 50% to 75% improvement occurred, and excellent when 75% to 100% improvement was noted. Follow-up periods varied from less than three months to more than one year. The results are expressed in terms of improvement noted at the last follow-up visit. In some cases greater or less improvement had been observed on earlier visits. In several cases of those classified as having had a poor response there had been observed initial improvement, with subsequent relapse; in others no response to treatment had occurred. Relapses commonly appeared in the period from two to six months after treatment.

Good to excellent results were obtained in 75%, or 24, of the 32 cases treated with aminopterin. Improvement was known to have been maintained for 6 to 12 months in 13, or 41%, of these 24 cases in which results were considered good to excellent, since the follow-up period in these cases extended over this time.

Of the 17 cases treated with amethopterin alone, only 4 of these, or 25%, had unsatisfactory results, but the follow-up period in these cases did not exceed six months except in 2 cases. Some of these may be expected to relapse as the observation period is prolonged.

In the 13 cases treated with both aminopterin and amethopterin all received aminopterin as their initial course. It was found that in all these cases the patients that responded to aminopterin also responded to amethopterin in about the same degree when this drug was given as a second course. The second course never was administered less than three months after the original course. The amount of response and the rapidity and duration of the remission obtained with the two drugs in the dosage schedules as described appeared almost identical as observed in the same patient. There was no evidence of loss of therapeutic efficacy in the second course. When the patient responded poorly to aminopterin, response was no better with amethopterin.

In some cases an additive effect of more than one course of either drug was observed, so that improvement was obtained after an additional course even three or more months after the original course. Cases that relapsed fairly rapidly after aminopterin relapsed just as rapidly after amethopterin.

Results at End of Observation Periods After Course of Treatment

	Poor (0%–50% Improvement)			Good (50%–75% Improvement)			Excellent (75%–100% Improvement)				
	Less than 3 Mo. of Observation	3–6 Mo. of Observation	6–12 Mo. of Observation	Less than 3 Mo. of Observation	3–6 Mo. of Observation	6–12 Mo. of Observation	Less than 3 Mo. of Observation	3–6 Mo. of Observation	6–12 Mo. of Observation	Total	Percentage
One course aminopterin (6 mg.)	3		1		1	2	5	1	4	17	47
One course amethopterin (30 mg.)	2			3	4		1	1	1	12	
One course either drug and additional therapy *	1	2	2	1	2	3	1	3	4	19	40
Two courses either drug	1	1	1			1			2	6	
More than two courses either drug						7			1	8	13
Totals	7	3	4	4	7	13	7	5	12		
Total		14			24			24		62	100

* Additional therapy is 4.5 mg. aminopterin or 22.5 mg. amethopterin.

From the above, the dosage of aminopterin, 0.5 mg., gave almost identical clinical results as amethopterin in five times this dosage, or 2.5 mg., when used in the manner described.

The Table is a compilation of all cases treated by the folic acid antagonists and of the results obtained at the end of the observation period. It can be seen that 48 (77.4%) of the cases had good (24) to excellent (24) results; 14 cases (23%) had poor results, that is, less than 50% clinical improvement. Twenty-five of the twenty-nine (86%) cases observed from 6 to 12 months were considered to have had satisfactory results; twenty-three of thirty-three cases (70%) observed less than 6 months had satisfactory results.

Age, sex, and duration of the disease had no relationship to the therapeutic results. Likewise, no relationship of results to type of psoriasis (guttate, plaque, or mixed, with or without pustular lesions of the plantar surfaces) was observed.

Of the 29 (47%) cases which received only one course of either drug, 23 had good (10) or excellent (13) results at the end of the observation period, which in 7 cases was more than six months. Of the 54 cases which had two or less courses of either drug or both, 38 had satisfactory results, as did the 8 that had more than two courses.

Toxic Effects and Adjuvant Therapy

Two cases treated with aminopterin exhibited toxic effects; one complained of her menstrual period being late 10 days, and the other complained of a mild sore mouth on the 5th day of her initial treatment course. Both of these and all the other patients in whom complete blood cell counts were performed before and after their course of treatment showed no significant change in their hematologic picture. No cases treated with amethopterin had any observable side-effects from their treatment courses. All patients were questioned directly regarding side-effects which might be expected, especially concerning symptoms of the tongue and mouth. The patients were directed to stop medication immediately on the appearance of any toxic symptom, especially a sore mouth or sore tongue. Two cases, not reported here, stopped therapy because of this admonition; one developed mumps while under treatment, and the other developed a sore throat.

The relatively low and almost nontoxic dosage schedule used in this study appears to be practical for the treatment of moder-

ately severe or severe cases of psoriasis, although the clinician must be alert to toxic effects and drug idiosyncracy which may occur in any patient taking folic acid antagonists. The toxic effect on fetal tissues must always be kept in mind, and the drug may be best not administered to women in the childbearing age. In all cases these potentially toxic drugs should be used cautiously and with good clinical control. All the cases reported here are private cases observed relatively frequently. As a means to help insure post-treatment observation, injections of 1000 mg. of cyanocobalamin (vitamin B_{12}) or 35 mg. of riboflavin were administered at two-week intervals for about three months after a course of treatment. It seems doubtful to us that this medication influenced the course of psoriasis, although it did afford a mechanism for post-treatment observation. Almost all the cases were using topically a mercury soap in motor-oil mixture, which is as effective as any standard topical application for psoriasis.

Summary and Conclusions

Sixty-two cases of psoriasis of moderate to severe degree were treated with aminopterin, amethopterin, or both. The results are recorded.

Thirty-two received aminopterin; seventeen received amethopterin, and thirteen were given both, in the dosage schedule outlined. Of those who received aminopterin alone, 75% had more than 50% improvement at the time of the last observation period, and the same percentage showed a similar degree of improvement after amethopterin. Of the 13 patients who received both drugs, 11 maintained more than 50% improvement until the last observation date.

A considerable number of those patients who went into a significant remission did so for periods ranging from three months to a year after their original course of treatment.

Toxic effects were rarely observed in this series, but considerable caution is required in the use of these drugs.

University Square No. 1, 4625 Fifth Ave. (13).

REFERENCES

1. Gubner, R.; August, S., and Ginsberg, V.: Therapeutic Suppression of Tissue Reactivity: Effect of Aminopterin in Rheumatoid Arthritis and Psoriasis, Am. J. M. Sc. 221:176-182 (Feb.) 1951.

2. Rees, R. B.; Bennett, J. H., and Bostick, W. L.: Aminopterin for Psoriasis, A. M. A. Arch. Dermat. 72:133-144 (Aug.) 1955.

3. Burchenal, J. H.; Karnofsky, D. A.; Kingsley-Pillers, E. M.; Southam, C. M.; Myers, W. P. L.; Escher, G. C.; Craver, L. F.; Dargeon, H. W., and Rhoads, C. P.: The Effects of the Folic Acid Antagonists and 2,6-Diaminopurine on Neoplastic Disease with Special Reference to Acute Leukemia, Cancer 4:549-569 (May) 1951.

The British National Health Service and Dermatology

PATRICK HALL-SMITH, M.D. (Edin.), M.R.C.P. (Lond. & Edin.), Hove, Sussex, England

In moments of informal discussion over the luncheon and coffee tables at the 11th International Congress of Dermatology in Stockholm, American colleagues and colleagues of other nationalities were interested to know something of the British National Health Service and the effect it has had on the practicing dermatologist. Many questions were asked, and it was soon realized that those outside Britain knew little about the organization of medicine in the United Kingdom since 1948, when our National Health Service was introduced. An American colleague felt that to be forewarned was to be forearmed, and it was on his suggestion that this brief review has been prepared. An attempt has been made to keep it as factual as possible, and its content, for the most part, is confined to the Health Service as it affects the specialist, in particular the dermatologist, and not the general practitioner.

Recruitment and Training of Dermatologists

Before 1948 the would-be consultant, during his period of specialist training and until a hospital consultant appointment fell vacant (a *sine qua non* for consultant practice in Great Britain), eked out a precarious livelihood on a small honorarium, coaching medical students for their examinations, and possibly limited private practice. Since the inception of the Health Service, the trainee specialist, after 18 months or 2 years of general internships, first becomes what is known as a registrar in his specialty for a period of two years, though he may be reappointed for successive periods in this grade. Although most registrars have as their ambition an eventual consultant career, only a proportion succeed in gaining promotion in the hospital service. These appointments are almost invariably full-time, and the salary range is around £1000 per annum ($2800).

After serving two years in this grade, more probably four and sometimes longer, the registrar will apply in open competition for an appointment as senior registrar, with a salary of £1500 ($4200), which is the real training grade for the future consultant. The normal tenure of a senior registrar post is four years, though the majority serve in this grade for a much longer period. There has been some abuse of this grade, particularly in general medicine and surgery, where a large number of senior registrars have been carrying consultant responsibilities but without the status and remuneration; to a smaller extent this applies in other specialties.

There is no specialist diploma or examination in dermatology for British dermatologists; however, in these competitive days to obtain even a registrar appointment in the skin department of a teaching hospital it is almost essential to have the M.R.C.P. diploma. This higher examination, conducted by the Royal College of Physicians of London, is in general medicine, and the pass rate is about 10% to 12%. The fact that one intends to become a dermatologist is of no interest to the examiners—all those intending to be specialists in any branch of medicine (as distinct from surgery) take the same examination; there is no choice of questions, which, in both the written and the clinical examination, favor those practicing general (internal) medicine or a specialty such as cardiology or neurology; it is rare for any specifically dermatological question

Submitted for publication Feb. 13, 1958.

to be asked. The Royal College of Physicians of Edinburgh may be regarded by some as more enlightened, as half their examination is taken in a special subject, e. g., dermatology, neurology, and the other half in general medicine. However, for those practicing in London and in the South of England, it is an advantage to have the London membership.

Consultant Appointments

At the end of his tenure as senior registrar, the prospective consultant will have been qualified for about 10 years, often very much more, and will be at least 32 years old. Owing to Army service and dearth of consultant vacancies, some prospective consultants have been 40 or more before they have obtained appointments.

With the exception of the teaching hospitals, which are largely autonomous (though the selection machinery for consultants is similar), the hospitals throughout Britain are divided on a regional basis and administered by a regional hospital board. These boards are the employers of the consultant, and it is they who decide when a hospital or group of hospitals requires a specialist in any branch of medicine or surgery; these appointments are advertised in the medical press and in the case of dermatology and most other specialties (the usual exceptions being pathology and sometimes radiology and venereology) are on a part-time or sessional basis. A maximum part-time appointment means working over 33 hours a week (9½ sessions) in the hospital service, which would bring in a salary of £1813 ($5050), rising by annual increments to about £2650 ($7420). If less time is spent in the hospital service, the salary would be proportionately less; some consultants with a flourishing private practice do not want to be hampered with too many hospital sessions.

Private Practice and Merit Awards

Anyone, regardless of his income, and any foreign visitor can obtain free specialist treatment through a hospital. There is no doubt that many patients who could well afford a private consultation take advantage of the Health Service, and I, who undertake one of my hospital sessions in a high-class residential district, see a number of patients who want their eczema cured or warts removed before they winter in Florida or the South of France; ". . . specialist treatment, you know, is so expensive abroad." All drugs and medicaments can be obtained for a nominal charge of 1/- (15¢) for each prescription, and some of these patients have no scruples about demanding a plentiful supply of hydrocortisone ointment or other costly medicament to tide them over their holiday. In all fairness, however, most patients are reasonable and are grateful for what is done for them.

Despite the over-all drop in the number of patients seeking private consultations, private practice is still very much alive in some areas, and there is no doubt that a few consultants are as busy in private practice as they were in the pre-Health Service era. In addition to his paid hospital work and private practice, the consultant may receive a possible "merit" award. These merit, or distinction, awards are of £500 ($1400), £1500 ($4200), and £2500 ($7000) per annum and are granted by the Minister of Health on the advice of a national committee of doctors and laymen; 20% of all consultants receive the lowest award; 10%, the second award, and 4%, the highest award. These awards are secret, and so it is impossible to say what percentage of dermatologists are in receipt of them; not all recipients, however, are averse to telling their friends that they have been lucky. These secret awards have been much criticized as invidious in a publicly administered medical service. One eminent physician is known to have refused his award on principle; needless to say, few have had the moral courage or financial independence to follow his lead. It can be seen, therefore, that the most

eminent and fortunate may have an income of £5000 ($14,000) from salaried sources alone before receiving anything from private practice, though it must be emphasized that this basic figure would apply to only 4% of consultants from all specialties.

The General Practitioner

It would be right to say that the majority of consultants are moderately well satisfied with the conditions and terms of their service, provided that they are working in an area which gives them an opportunity for private practice. This cannot be said of those senior registrars who are overdue for a consultant appointment; most certainly it cannot be said of many general practitioners, who have threatened mass withdrawal from the Service on more than one occasion. For the majority of general practitioners private practice has virtually disappeared; the general practitioner is paid an annual capitation fee of about 17/- ($2.50) for each patient on his list. No matter how much time the doctor spends on his patient or how many visits he makes, the sum remains the same—he is not paid for each item of service. He is limited in the number of National Health Service patients he can have on his list; the average net earnings of a general practitioner are around £2000 ($5600) per annum.

Comment

The organization of medicine in Britain is still in a stage of transition, and only time will tell the final effects of the Health Service on the individual doctor and his patients. Although there is much good in our system—for example, the availability and high standard of specialist care in all parts of the country—there is no doubt that grave mistakes were made by our leaders in their negotiations with the Government in 1948. If we had known then what we know now, our present system would be different, and we would have protected ourselves from the politicians; both our great political parties have been guilty of political auctioneering with ever more grandiose schemes for the welfare state, and neither the standing of British medicine nor our profession has been enhanced by these activities.

65, The Drive.

Giant Keratoacanthoma

ANDREW KALLOS, M.D., New York

The concept that tumor-like keratoses of Poth,[1] primary self-healing squamous-cell epithelioma of the skin,[2] and keratoacanthoma[3] are variants of the same disease is steadily gaining ground.[4] Rapid development, benignity, and spontaneous involution with scarring and typical pathology are common to all three types of tumors. There are, however, a number of divergent elements in the three entities which have to be elucidated upon before this unicist theory can be recognized as final.

On the other hand, familial incidence is present only in the primary self-healing squamous-cell epithelioma of the skin. The multiplicity of lesions, their recurrence, or a chronic clinical course are witnessed in the tumor-like keratoses of Poth and in the primary self-healing squamous-cell epithelioma of the skin. The face is the usual site for keratoacanthoma, which develops as a single lesion, grows to the largest size, and occurs in the fifth or sixth decades of life. These distinctive features are rather constant and help in establishing the diagnosis for each variety, should varieties still be recognized.

Predisposing factors, such as blistering sunburn, long-continued exposure to tars and shale oil, and arsenic intake, vary in the different case reports or are completely lacking; hence, they cannot be relied upon. A tempting virus etiology, while strongly supported by an otherwise extensive parallel between these conditions and the verrucae, could not be ascertained, since inoculation experiments, so far, have failed to reproduce the disease.

Submitted for publication March 12, 1958.

From the Department of Dermatology, New York Polyclinic Medical School and Hospital.

The development of a large growth on the upper eyelid can lend the patient a frightful appearance, and it can interfere with his vision, as happened in my case.

A 57-year-old white man, signal operator for a railroad, developed a small boil-like lesion in the left eyebrow. Little matter was obtained on squeezing the node, and several intramuscular injections of penicillin failed to halt its growth. There was no itching, and the patient experienced no pain. When the patient was first seen by me,* about eight weeks after the onset (Fig. 1), there was restriction in the movements of the left upper lid. The tumor was round, 25 mm. in diameter. The skin was stretched over the abruptly sloping border, which was hard and yellowish-white. The top, 6 mm. above the base, was flat and covered with a dry solid brown crust. The tumor was not tender and could be easily moved, and the surrounding skin was not infiltrated. No lymph nodes were palpated in the submaxillary region.

The past history was negative for skin tumors; no acne or boils were recalled. The patient has been an outdoor switch operator for over 20 years,

Fig. 1.—Keratoacanthoma of the upper eyelid.

and the trains have been diesel-engine driven. He presented a healthy rosy complexion, but his skin was not weatherbeaten and there were no keratoses. The scalp showed loss of hair, of the male baldness type. He has been using bifocal lenses in a plastic frame.

After the covering crust was lifted, a crumbling semisolid amorphous material was found. Histo-

* The patient was referred by Dr. John R. O'Sullivan.

Fig. 2.—Crater after the removal of the central mass.

surface epidermis. The cells extend directly to the lateral border of the specimen. The history of rather rapid growth and unusual clinical presentation, plus the high degree of tumor-cell differentiation, would be most unusual in a squamous-cell epithelioma. These findings, however, are characteristic of the keratoacanthoma, which histologically is often confused with an epithelioma (Stanley J. Kallman, M.D.).

Curettage and fulguration of the growth yielded no lasting improvement; the border regrew to its previous height in eight days, and the central depression began to fill up anew. The whole lesion was treated from then on with biweekly applications of podophyllum, 25% in benzoin tincture,

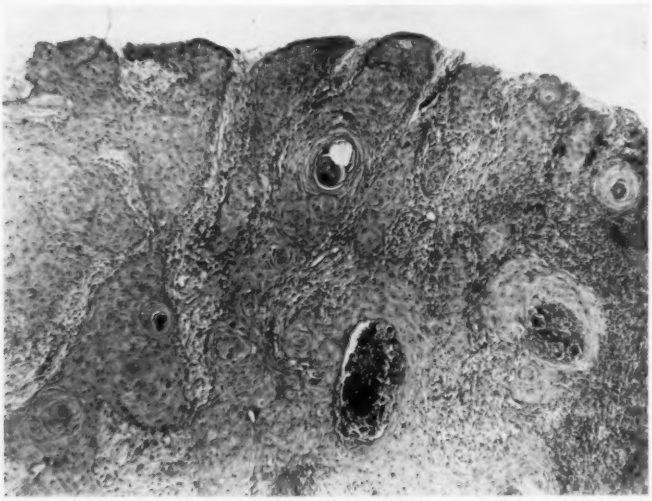


Fig. 3. — Histological section from the border of the growth.

logical preparation showed this material to consist almost entirely of masses and whorls of lamellated keratin and parakeratin; in a few areas, there were rounded groups of degenerated prickle cells; clotted blood was also noted; no molluscum bodies were seen. As the next step, the central mass was removed, exposing a deep crater (Fig. 2) with a few minute bleeding points. Report of the histological examination of a segment through the raised border read as follows (Fig. 3): The walls are lined by irregular-shaped masses of pseudoepitheliomatous squamous cells which bear a remarkable resemblance to a bonafide Grade 1 squamous-cell epithelioma. The tumor cells are well differentiated and form thick interwoven bands, within which intraepithelial collections of neutrophils and a few keratin pearls are seen. An intense chronic inflammatory reaction is present in the adjacent stroma. The hyperplastic squamous cells fill the corium and undergrow the overlying

over a period of 12 weeks. The response to this treatment was most gratifying from the start. The border of the lesion shrank gradually and disappeared, and the central part became epithelized; there remained, finally, a depressed atrophic area surrounded by an overhanging, slightly indurated

Fig. 4.—Healed lesion.

edge. The eyebrow was lost in its lateral third (Fig. 4).

Comment

The growth involved the major part of the lateral half of the upper eyelid. It was conspicuous and unsightly, and it interfered with the patient's vision. It did not change in size during four weeks of observation. Spontaneous involution, under these circumstances, could not be relied upon; some immediate measures had to be instituted. Superficial curettage and desiccation were unsuccessful. A wider and deeper surgical excision, on the other hand, would have caused the loss of a good part of the eyelid. The use of x-rays would have necessitated the insertion of a protective eyeshield—in this instance, a difficult maneuver. Podophyllum, as stated in numerous papers in the literature, has been used with good results in a great variety of skin growths, such as venereal warts, the growth of Molluscum contagiosum, keratoses, and even epitheliomas. Similarly, favorable results were claimed for keratoacanthoma.[5,6] It was most reassuring to see the prompt improvement that followed the very first application of podophyllum in my patient; spurts of renewed activity in the tumor were noted when these applications were withheld on two occasions, for 15 and 8 days, respectively. The complete involution of the keratoacanthoma seemed to prove the effectiveness of the therapeutic approach. The patient has been under observation for eight months without any sign of recurrence.

870 Fifth Ave. (21).

REFERENCES

1. Poth, D. O.: Tumor-like Keratoses: Report of a Case, Arch. Dermat. & Syph. 39:228, 1939.

2. Ferguson Smith, J.: A Case of Multiple Primary Squamous-Celled Carcinomata of the Skin in a Young Man, with Spontaneous Healing, Brit. J. Dermat. 46:267, 1934.

3. Rook, A. J., and Whimster, I. W.: Le Kérato-acanthome, Arch. belges. dermat. et syph. 6:137, 1950.

4. Ereaux, L. P.; Schopflocher, P., and Fournier, C. J.: Keratoacanthomata, A. M. A. Arch. Dermat. 71:73, 1955.

5. Calvert, H. T.: In discussion on Whittle, C. H. and Lyell, A.: Molluscum Sebaceum, (Kerato-Acanthoma, Benign Epithelioma), Brit. J. Dermat. 64:424, 1952.

6. Beare, J. M.: Molluscum Sebaceum, Brit. J. Surg. 41:167, 1953.

Asthma Melanodermica

Report of a Third Case, with Investigations

L. J. A. LOEWENTHAL, M.D., M.R.C.P., D.T.M. & H., and S. SHAPIRO, M.B., B.Ch., Johannesburg, Union of South Africa

Melanoderma associated with asthma was reported by Herraiz [1] in 1945. He stated that several patients had previously mentioned darkening of the skin accompanying asthmatic attacks and was able to verify this phenomenon in two personally observed females in Argentina. We have been able to observe a further similar case at intervals for over two years.

Report of Case

The patient was a 64-year-old widow.

Race.—In veiw of the mixed nature of the population of the Union of South Africa, this was carefully assessed. Her maternal grandparents were Portuguese; the others, Afrikaans. Afrikaans South Africans are whites of mixed Dutch and Huguenot French descent; miscegenation with the indigenous population cannot be excluded but would be so far removed in time as to be of little importance. She was always an olive-complexioned brunette, and we have seen a wedding photograph from 1914 in which her coloring was lighter than that of her husband, both being of normal European tint. She shows no negroid features such as flattened nose, everted lips, prognathism, or ulotrichous hair.

Family History.—She is one of six siblings; among these, and also among her other relations, there is no known case of increased pigmentation, asthma, or allergic disease of any kind. She has one normal daughter, an olive-complexioned brunette whom we have seen, and six normal grandchildren.

History of Present Complaint (December, 1957).—(*a*) Asthma: About September, 1953, the patient noticed that her skin was becoming gradually darker. Three months later she had her first attack of asthma and was admitted to this hospital and treated with intravenously administered corticotropin (ACTH), with good results. She was readmitted with further attacks, and in November, 1954 (the first available record), it was noted that her skin was markedly pigmented. Conventional treatment failed to relieve her asthma, and she was again given corticotropin, with success. Her subsequent history is one of repeated admission at increasingly frequent intervals and of being tided over severe acute attacks of asthma with steroid therapy. In October, 1955, one of us was asked to see her, and the description of similar cases by Herraiz came to mind. For the last nine months right ventricular cardiac failure has been readily precipitated during acute attacks; she now has effort dyspnea, orthopnea, and paroxysmal nocturnal dyspnea, even between attacks.

(*b*) The Skin: She has observed that each asthmatic attack is preceded by three or four days of gradual darkening of the skin. Simultaneously her urine and her feces become darker, and she states that she can forecast an attack of asthma from these alone. Throughout the years her skin has been noticeably darker on admission during asthmatic attacks and considerably lighter within a few days of remission. Since the onset of her illness her dermal nevi have increased in number and size, chiefly over the face, arms, and upper trunk, and have also become darker before each attack. During the same period the hair has become sparse over the vertical and frontotemporal regions; no change has been observed in its texture or color.

Clinical Findings.—We have seen this patient repeatedly over the years, both during and between attacks of asthma. During remission her skin was formerly that of a European brunette, but lately it has been darker even during this phase. When she is admitted during acute attacks her skin universally is considerably darker and she is taken at first sight to be a member of one of the colored races, equivalent to a moderately dark Indian and arousing unfavorable comment among the more prejudiced white patients in the ward (Fig. 1).

The genitalia are not disproportionately pigmented, and there is no pigmentation of the oral mucous membrane visible to the naked eye on examination. The scalp hair is somewhat sparse over the frontotemporal and vertical areas but

Submitted for publication Feb. 14, 1958.

From the Johannesburg General Hospital.

Fig. 1.—Patient's hands, shortly after an asthmatic attack, compared with that of a medium-colored Caucasian.

not sufficiently to excite comment in a woman of her age.

The face shows numerous lentigines, which the patient states have appeared in the last few years (Fig. 2). Hairy and nonhairy heavily pigmented dermal nevi are present in considerable numbers; these have been seen to darken during an attack.

No other abnormalities were found on clinical examination; the blood pressure was consistently normal (120/70, 150/90, 130/80, etc.).

Fig. 2.—Pigmentation, lentigines, and large dermal nevi; photograph taken at same time as Figure 1.

Investigations.—The suspicion that this was not just a straightforward case of bronchial asthma was first mooted by Dr. P. Smith, in April, 1955. He found the serum iron normal, ruled out porphyria, and attempted to withhold steroids in order to assess adrenal and pituitary function. However, this proved impossible, since her asthma became intractable and dangerously distressing. Ever since, the patient has been given erratic steroid therapy. After a month or two she generally defaults from attendance at the outpatient department, stops taking steroids, and is admitted to hospital shortly after with an acute attack.

The Table presents the investigations that have been made from time to time; most of these were done during or shortly after an acute attack. In addition, numerous roentgenograms of the chest, electrocardiograms, and examinations of the stools and urine for parasites and ova were noncontributory. Attention is drawn to the following points:

1. There was no evidence of hemochromatosis, hemosiderosis, porphyria, schistosomiasis, or parasitic infestation of the lungs.

2. Eosinophilia of up to 11% eosinophils usually accompanied attacks, and eosinophils were twice observed in the sputum.

3. There was no evidence suggestive of bronchiectasis or tuberculosis.

4. The skin biopsy specimen showed an increase of melanin in the basal-cell layer compared with the skin of a Caucasian brunette; pigment was present also in the rete Malpighii. Chromatophores and hemosiderin were not seen in the dermis. The section would have excited no comment if taken from an Indian or a light-colored Negro.

Unfortunately, we obtained a history of darkening of the urine and stools preceding attacks one

Summary of Laboratory Investigations

	Blood												Urine					Stool	Sputum
Date	Total Leukocytes	Eosinophils, %	Sedimentation Rate, Mm/Hr.	Urea, Mg/100 Ml.	Na, mEq/L.	K, mEq/L.	Chlorides, mEq/L.	CO_2, mEq/L.	Serum Iron, μg/100 Ml.	Sugar, Mg/100 Ml.	Serum Melanin	Liver Function Tests *	Kahn Test	Centrifuged Deposit	Porphyrins	Iron	Melanin	24 Hr. Vol., Ml.	17-Ketosteroids, Mg.	17-Ketogenic Hormone, Mg.	Melanin	
8/54	6800	10.5												Nil								α-Hemolytic streptococci Neisseria catarrhalis
12/54	6000	6							283	63		All Normal				Absent						
4/55									128						Absent							
6/55				30	139	4.4	99	24.6							Absent							
10/55	5300	11	7	29																		
11/55																		1940	3.6			
12/55	4700	9.5	23										Neg.									α-Hemolytic streptococci Neisseria catarrhalis Diphtheroids
4/56																						α-Hemolytic streptococci Neisseria catarrhalis
5/56	4200	1		28																		
7/56				78	133		85	22.4										600	2.0			Neisseria catarrhalis Pneumococci Diphtheroids Eosinophils
2/57	4000	12	21										Neg.									
3/57																						Klebsiella pneumoniae Pneumococci Staphylococcus pyogenes var. aureus
5/57	4500	2	29	42																		α-Hemolytic streptococci Eosinophils
8/57	2200	5	8	46										Nil								No tubercle bacilli
10/57				52	143	4.0	97	26.7														No tubercle bacilli
11/57 †											Absent						Absent	1670	3.2	12.6	Absent	

* Thymol turbidity, thymol flocculation, colloidal red, cephalin cholesterol flocculation, Takata-Ara reaction, zinc sulfate turbidity, total lipid, alkaline phosphatase (King-Armstrong), van den Bergh reaction, direct and total bilirubin, albumin, globulin, γ-globulin, serum cholinesterase.

† One week after end of asthmatic attack.

week after having broken her last attack only; on previous admissions an exhaustive history had not been taken, because she was regarded simply as having chronic asthma with an acute exacerbation. It is important to note that the complete history was taken at the last admission and that no leading questions were put; the story of darkening of the urine and stools was volunteered by the patient, and by that time melanin and precursors could not be detected in the serum, urine, or stools. We are expecting another attack and shall add the findings if the patient returns to our care at the proper time.

Comment

Herraiz suggested no mechanism for the pigmentation in his cases of otherwise typical bronchial asthma. We are unable to do more than point to certain features of the case which may be relevant.

1. The occurrence of initial hyperpigmentation was followed after three months by the first attack of asthma, and the increase of pigmentation and darkening of the stools and urine invariably precedes asthmatic attacks, and so the patient can predict the onset of attacks. We feel that we can, therefore, exclude the possibility of pigmentation resulting from endocrine imbalance caused by the stress of an asthmatic attack. Such endocrine studies as have been possible produced normal results.

2. The notable increase in the number, size, and pigmentation of dermal nevi and lentigines strongly suggests that the increase in pigmentation is effected by increase of, or lack of opposition to, the melanocyte-stimulating hormone.[2,3]

3. The cases described by Herraiz were reported as examples of typical bronchial asthma of probable allergic causation; the pigmentation was apparently an incidental finding. In our case, too, there was nothing to distinguish the asthma per se from the usual pattern. Skin tests for allergy were not done.

Summary

A third case of asthma melanodermica is presented.

Investigations gave no information regarding the nature of the relationship between the asthma and the cutaneous pigmentation and increase of moles. Clinically, however, there is an invariable sequence of pigmentation followed by an asthmatic attack.

Dr. M. M. Suzman allowed us to publish the case. The photographs are by Dr. Bensusan, Department of Medicine, W. W. Rand University.

604, Medical Centre, 209, Jeppe St.

REFERENCES

1. Herraiz, I.: Asma melanodérmica, Rev. argent. dermatosif. 27:455, 1945.

2. Lerner, A. B.; Shizume, K., and Fitzpatrick, T. B.: On the Mechanism of Melanin Pigmentation in Endocrine Disorders, J. Invest. Dermat. 21:337, 1953.

3. The Pituitary and Pigmentation, Lancet 1:392, 1955.

Pruritus and Proteolytic Enz ·es

SAMUEL MONASH, M.D., and J. FREDERICK WOESSNER Jr., Ph.D., Miami, Fla.

It has been stated recently by Shelley and Arthur [1-3] that there is a causal relationship between pruritus and proteolytic enzymes. Cormia et al.[4] support this theory. The principal argument in its favor is the fact that certain proteolytic enzymes, when applied externally by injection, surface application, or scratch testing, are pruritogenic. While it may be true that the mechanism of pruritus is bound up in some way with enzymic action, as are so many other vital processes, it seems to us that the question as to whether the sensation of pruritus is caused by the proteolytic action of enzymes must be reexamined critically. Our experiments tend to show that pruritus can be produced by inactivated enzymes, devoid of any enzymic activity.

Methods in Scratch Tests with Various Proteolytic Enzymes

The enzymes were diluted in the buffered phosphate saline solution recommended by Arthur and Shelley,[1] except the lyophilized trypsin, which was dissolved in isotonic saline. Most of the experiments were performed upon one of the authors but subsequently were repeated on dermatologic associates and other volunteers. Testing was limited to the anterior surfaces of the arms and forearms.

Cowhage spicules were not available at the time this work was started, and various other methods of introducing the enzyme into the skin were used. A very thin needle was inserted through a drop of the solution as superficially and as parallel to the surface of the skin as possible. This method did not produce reliable results, probably because of the variation in the amount of liquid adhering to the needle. Scratching a cross mark on the skin through a drop of the solution proved satisfactory and reproducible. Since a dilution of 1:1000 of the enzymes seldom produced an itch, dilutions of 1:10 and 1:100 were used. On skin stripped with cellophane (Scotch) tape, simple application of the solution to the stripped skin was made.

Ficin and papain (obtained from the Nutritional Biochemicals Corp., Cleveland, Ohio) were used in most of the tests because they regularly produced severe itching lasting at least eight minutes, whereas the other enzymes were much less pruritogenic. In some cases pancreatin was used.

Dry papain, ficin, and pancreatin were heated for two hours in a hot-air oven at 125 C. A 1:10 solution of these heated enzymes was then tested for pruritogenic activity with the scratch test.

Another method of inactivating the enzymes employed was heating 1:10 dilutions to 100 C for 45 minutes. The solutions were then tested with the scratch test and also assayed for proteolytic activity by the hemoglobin assay method of Anson.[5]

The dry enzymes, after being heated at 125 C for two hours, were dissolved in the buffer solution in 1:10 dilution and then placed upon skin stripped 15 times with cellophane tape, and the severity and duration of itch were noted.

Crystallized lyophilized trypsin (labeled minimum activity, 8000 units per milligram) was obtained from the Worthington Biochemical Corp., Freehold, N. J. The dry crystals of trypsin were heated at 140 C for two hours. The heated product remained white and water soluble. The trypsin preparations were assayed by the method of G. W. Schwert and Y. Takenata,[6] with use of N-benzoyl-L-arginine ethyl ester (BAEE) as substrate. The activity of the unheated trypsin was 6250 units per milligram, and that of the heated trypsin was only 5 units per milligram, showing that the heated trypsin had been almost completely inactivated. Nine persons were given intracutaneous injections on the forearms of 0.03 ml. of 1:1000 unheated trypsin solution in isotonic saline. Four of the same persons and five others were given similar injections of 1:1000 heated trypsin solution in isotonic saline.

Methods with Mucuna Pruriens Spicules

Arthur and Shelley [1] tested the pruritogenic activity of Mucuna spicules by inserting a single spicule into the skin as nearly parallel to the surface as possible

Submitted for publication Feb. 14, 1958.

From the Division of Dermatology, Department of Medicine, University of Miami School of Medicine (Dr. Monash), and the Howard Hughes Medical Institute (Dr. Woessner).

and noting the reaction. We were unable to obtain consistent itching with this technique. The spicules are very small, and an individual spicule does not always produce itching. This may be because it may not pass through the itching points referred to in one of the more recent reports of Shelley and Arthur.[7]

The method we used to determine whether the spicules were pruritogenic was to rub a number of them, approximately 10, back and forth on a small area of the skin of the forearm for 10 seconds. This procedure consistently produced itching with pruritogenic spicules.

Preparation and Assay of Enzyme Mucunain

Extracts of Mucuna spicules were prepared in the manner outlined by Shelley and Arthur.[8] Eight milliliters of 0.9% NaCl was added for each gram of spicules. The spicules were mashed in a mortar with the saline solution until they became thoroughly wetted. The mash was filtered through Whatman No. 1 paper, with use of a Buchner funnel and a vacuum pump. All steps were carried out in the cold. The enzyme was precipitated by the addition of alcohol, washed, and redissolved.

Assays of proteolytic activity were done by the following methods:

1. Hemoglobin method of Anson[6]; the composition of the digestion mixture was 3.0 ml. 2% hemoglobin solution pH 7.4, 1.0 ml. 0.1 N phosphate buffer pH 7.4, 1.0 ml. Mucuna extract. This mixture was incubated at 37 C for 30 minutes.

2. Casein digestion method of Kunitz.[8]

3. Alcoholic KOH titration method of Grassman and Heyde,[9] used to assay hydrolysis of glycylglycine, carbobenzoxyglycyl-L-phenylalanine, and carbobenzoxyl α-glutamyl-L-tyrosine.

The dry spicules were assayed for proteolytic activity before being heated and after being heated in a dry oven for two hours at 100 C, two hours at 125 C, three hours at 125 C, six hours at 125 C, and one and one-half hours at 140 C. They were then tested for pruritogenic activity.

A batch of Mucuna pruriens pods arrived from Jamaica in a wet container. After they were dried, the spicules proved to be nonpruritogenic. They were then tested for the presence of mucunain and for their proteolytic activity.

Results with Scratch Tests

Scratch tests with various enzymes produced itching of varying intensity and duration (Table 1). Scratch tests with 10% solutions of the powdered enzymes papain, ficin, and pancreatin readily produced itching although the enzymatic activity of the preparations had been destroyed by treatment with dry heat at 125 C for two hours (Table 2).

TABLE 1.—*Results of Scratch Tests with Enzymes*

Substances	Concentration	Time Interval Before Itching, Min.	Intensity of Itch	Duration of Itch, Min.
Ficin in buffer solution	1:100	1	Severe	13
Papain in buffer solution	1:100	¼	Severe	9
Pancreatin in buffer solution	1:10	2	Mild	3
Chymotrypsin in buffer solution	1:10	3	Mild	2

Scratch tests with 10% solutions of the enzymes papain, ficin, and pancreatin heated to 100 C for 45 minutes produced itching approximately the same as unheated enzyme solutions (Table 3). By this procedure, papain was 100% and ficin, 99.9% inactivated.

TABLE 2.—*Effect of Heating Dry Enzyme at 125 C for Two Hours and Subsequent Scratch Testing of Enzymes in Concentration Indicated*

Substance	Concentration	Before Heating	After Heating
Papain	1:10	Severe itch for 10 min.	Severe itch for 15 min.
Ficin	1:10	Severe itch for 15 min.	Severe itch for 6 min.
Pancreatin	1:10	Mild itch for 4 min.	Mild itch for 2 min.

Ten per cent solutions of the dry enzymes, papain, ficin, and pancreatin, which had been inactivated by being heated to 125 C for two hours, when placed upon skin stripped 15 times with Scotch tape

TABLE 3.—*Effect of Heating Solutions of Enzymes at 100 C for Forty-Five Minutes and Subsequent Scratch Testing*

Substance	Concentration	Before Heating	After Heating
Papain	1:10	Severe itch for 10 min.	Severe itch for 11 min.
Ficin	1:10	Severe itch for 15 min.	Severe itch for 25 min.
Pancreatin	1:10	Mild itch for 4 min.	Mild itch for 5 min.

TABLE 4.—*Results of Application of Solutions of Enzymes Heated at 125 C for Two Hours on Skin Stripped Fifteen Times with Cellophane (Scotch) Tape*

Substance	Concentration	Before Heating	After Heating
Papain	1:10	Severe itch for 13 min.	Severe itch for 15 min.
Ficin	1:10	Severe itch for 16 min.	Severe itch for 20 min.
Pancreatin	1:10	Mild itch for 2 min.	Mild itch for 1 min.

produced as much pruritus as before (Table 4).

Of the nine persons tested with intracutaneous injections of 1:1000 lyophilized unheated trypsin solution, five reacted with itching lasting two and one-half to five minutes; one, with a burning sensation, and three, with no sensation at all. Four of the five reactors with unheated trypsin solution also received injections with the heated trypsin solution, and all reacted with itching lasting two to four minutes. Of five other persons receiving the heated trypsin injections, three reacted with itching lasting one to two minutes; one, with a burning sensation, and one did not react.

Results with Spicules of Mucuna Pruriens

Mucuna extracts produced a small amount of hydrolysis of glycylglycine and carbobenzoxyl glutamyl-tyrosine, thus supporting the chromatographic studies of Shelley and Arthur,[3] but produced no hydrolysis of carbobenzoxyglycyl-phenylalanine after a two-hour incubation.

The Mucuna spicules were very resistant to loss of proteolytic activity by dry heating. As shown in Table 5, it required six hours at 125 C or one and one-half hours at 140 C to inactivate them. Their pruritogenic activity after inactivation was approximately the same as before heating.

The moist batch of Mucuna spicules was allowed to dry at room temperature. The spicules were not pruritogenic when dry. When assayed for content of proteolytic enzyme they showed approximately the same amount of proteolytic activity as the pruritogenic spicules.

Comment

The present studies fail to show a parallelism between proteolytic activity of substances, scratched or injected into the skin or applied to stripped skin, and their pruritogenic activity. The enzymes ficin, papain, and pancreatin remained pruritogenic although their enzymic activity had been almost completely destroyed by heat.

The pruritogenic activity of Mucuna pruriens spicules is probably not due to the enzymic activity of mucunain because (1) such activity persists despite exposure to a degree of heat which inactivates the enzyme and (2) enzymic proteolytic activity persists in spicules which have become nonpruritogenic after prolonged exposure to moisture.

TABLE 5.—*Effect of Dry Heating on Mucuna Spicules* *

Treatment of Spicules Before Extraction	Optical Density at 660 μ in Hemoglobin Assay
No treatment	0.590
Heat 2 hr. at 100 C	0.580
Heat 2 hr. at 125 C	0.110
Heat 3 hr. at 125 C	0.082
Heat 6 hr. at 125 C	0.025
Heat 1.5 hr. at 140 C	0.020

* Casein assay gave similar results; however, the casein method did not prove too satisfactory for assay of mucunain because of lack of linearity in amount of digestion at different enzyme levels.

Summary

The proteolytic enzymes ficin, papain, pancreatin, and chymotrypsin, when tested by scratch testing in a concentration of 1:10 to 1:100 in buffer solution, produce pruritus diminishing in intensity in the order given.

The pruritogenic character of the enzymes ficin, papain, and pancreatin is not lost when their proteolytic activity is destroyed by heating dry at high temperatures or by boiling their solutions.

The pruritogenic activity of a 1:1000 concentration of lyophilized trypsin in isotonic saline is still present even though the dry enzyme is inactivated by being heated at 140 C for two hours.

The mucunain enzymatic activity and the itch-producing action of the spicules of

Mucuna pruriens are separable. The spicules do not lose their pruritogenic character when they are heated dry at temperatures high enough to destroy their proteolytic capacity. The enzyme is very resistant to heat, requiring one and one-half hours at 140 C for complete inactivation. The spicules are no longer pruritogenic after prolonged exposure to moisture which does not destroy their enzymatic activity.

Dr. Harvey Blank cooperated and gave suggestions in carrying out this work. Dr. F. W. Jacobson and Prof. A. D. Skelding, both of the University College of the West Indies, Jamaica, B. W. I., and Felipe Gonzalez, horticulturist, of Harvard University, Atkins Garden and Research Laboratory, Cienfuegos, Cuba, supplied Mucuna pruriens pods.

Division of Dermatology, University of Miami School of Medicine.

REFERENCES

1. Arthur, R. P., and Shelley, W. B.: The Role of Proteolytic Enzymes in the Production of Pruritus in Man, J. Invest. Dermat. 25:341, 1955.

2. Arthur, R. P., and Shelley, W. B.: Experimental Evidence for an Enzymatic Basis for Itching in Man, Nature, London 175:901, 1955.

3. Shelley, W. B., and Arthur, R. P.: Studies on Cowhage (Mucuna Pruriens) and Its Pruritogenic Proteinase, Mucunain, A. M. A. Arch. Dermat. 72:399, 1955.

4. Cormia, F. E.; Dougherty, J. W., and Unrau, S. A.: Proteolytic Activity in Dermatoses, J. Invest. Dermat. 28:425, 1957.

5. Anson, in Methods in Enzymology, Vol. 2, edited by S. P. Colowick and N. O. Kaplan, New York, Academic Press, Inc., 1955, p. 3.

6. Schwert, G. W., and Takenaka, Y.: A Spectrophotometric Determination of Trypsin and Chymotrypsin, Biochim. et biophys. acta 16:570, 1955.

7. Shelley, W. B., and Arthur, R. P.: Studies on Pruritus, Tr. A. Am. Physicians 69:285, 1956.

8. Kunitz, in Methods in Enzymology, Vol. 2, edited by S. P. Colowick and N. O. Kaplan, New York, Academic Press, Inc., 1955, p. 32.

9. Grassman and Heyde, in Methods in Enzymology, Vol. 2, edited by S. P. Colowick and N. O. Kaplan, New York, Academic Press, Inc., 1955, p. 100.

The Mechanism of Solar Carcinogenesis

A Study of the Role of Collagen Degeneration of the Dermis in the Production of Skin Cancer

BRUCE S. MACKIE, M.B., B.S., D.D.M., and VINCENT J. McGOVERN, M.D., Sydney, New South Wales, Australia

The association of cutaneous malignancy with degenerative changes of the dermis, in areas exposed to the sun, is frequently observed. This has led us to inquire into the nature of the relationship which exists between the two conditions.

1. Physiological Considerations

As it is the intention of this paper to deal with conditions which arise from long-term exposure to solar radiation, it is necessary to consider certain physiological aspects bearing upon the main theme. The discussion will primarily involve responses to ultraviolet light, as other wavelengths seem to have no photobiological activity.

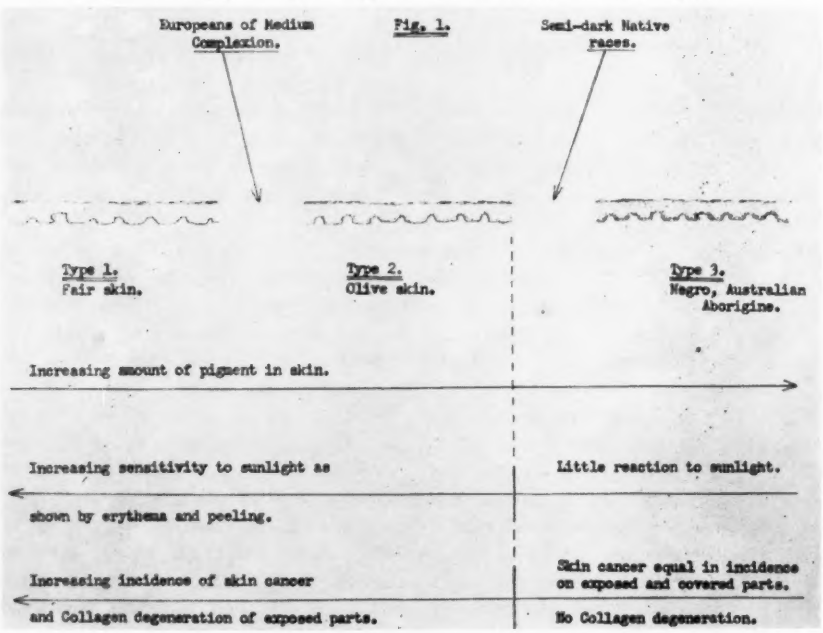
Classification of Skin Types.—The first point is our own division of humans into three main types, depending on the degree of pigment in their skin, although all variations in grade between these types occur (Fig. 1).

Type 1, the fair-complexioned person, has little or no natural (inherent) pigment

Received for publication Jan. 16, 1958.

Dermatological Department (Dr. Mackie) and Fairfax Institute of Pathology (Dr. McGovern), Royal Prince Alfred Hospital.

Fig. 1.—The pigmentary skin types and their reactions to solar exposure.


Europeans of Medium Complexion.
Fig. 1.
Semi-dark Native races.
Type 1. Fair skin.
Type 2. Olive skin.
Type 3. Negro, Australian Aborigine.
Increasing amount of pigment in skin.
Increasing sensitivity to sunlight as shown by erythema and peeling.
Little reaction to sunlight.
Increasing incidence of skin cancer and Collagen degeneration of exposed parts.
Skin cancer equal in incidence on exposed and covered parts.
No Collagen degeneration.

in his skin and little tendency to form more after exposure to ultraviolet light (UVL), although he may freckle. Type 2, the olive-skinned person, has a certain amount of natural pigment in his basal layer and readily develops more after exposure to UVL. In this type there is only a little pigment in the epidermis above the basal layer, most of it dropping into the dermis rather than passing to the surface. Type 3, the dark-skinned person, has a great deal of natural pigment in all layers of his epidermis. It is the range from Type 1 to Type 2 that is of particular interest in the present study, since the remaining dark-skinned races do not suffer from the solar form of skin cancer.

The cutaneous reactions to UVL are erythema, pigmentation, and thickening of the stratum corneum. In our discussion of these reactions, the importance of recognizing skin pigmentary types will become apparent. We intend to omit any discussion of vitamin D synthesis, as there is no serious suggestion that it plays any part in carcinogenesis.

Erythema.—Erythema following exposure to UVL occurs after a latent period of several hours, is bright red, and varies in intensity from a mild flush to edematous and blistered burns. The degree of erythema is directly dependent on the dose and is greater in people with fair skin. Persons of Type 1 redden with small doses, while those of Type 2 burn only with heavy exposure.

The simplest explanation of these facts is the suggestion that erythema is due to a direct effect of UVL upon the vessels of the subpapillary vascular plexus. In making this statement, we have given full consideration to the opinions of Blum (1940 et seq.), Laurens (1942), Kovács (1945, 1950), and others who believe that erythema results from a photobiological reaction in the prickle-cell layer with subsequent permeation of vasodilator protein breakdown products to the blood vessels of the dermis. Their theory fails to explain why the presence of melanin in the basal layer increases the erythema dose to such a degree.

Pigmentation.—The second phenomenon is that of pigmentation, the ability to develop melanin increasing in different European skin types from almost nil in Type 1 to a maximum in Type 2. Within this range of skin types, pigment is found in the basal layer and the upper dermis but there is little in the prickle cells, the granulosa, or the corneum. Thus, when pigment is present, it offers little protection to the epidermis but it does protect the dermis and, as melanin absorbs more in the short wavelengths than in the long (Edwards and Duntley, 1939), it protects the dermis more from UVL than from any other wavelength. This point is also supported by the finding that the pigment of the basal layer has an absorption peak at 3000 A. in the solar spectrum (Bachem and Reed, 1931). We have observed that the repeated small suberythema doses experienced by an average resident of Sydney during everyday life are sufficient to maintain a moderate degree of tanning of the uncovered skin of persons of Type 2 and those intermediate between Types 1 and 2. Any pigment developed by subjects of Type 1 under these conditions is irregularly scattered in freckles.

Pigmentation appears to be the result of a primary action of UVL on the basal layer, although it could be consequent to an action on the dermis. Furthermore, the wavelength most potent in causing erythema and pigmentation correspond with those responsible for skin cancer in mice and lie within the range from 2900 A. to 3200 A. (Luckiesh and Taylor, 1939; Rusch, Kline, and Baumann, 1941; Blum, 1948).

Cornification.—The third physiological response to UVL is thickening of the stratum corneum. According to Blum (1942), who has studied extensively the effect of UVL on the epidermis of albino mice, the thickening of the corneum in these animals reaches its maximum about

one week after exposure and remains indefinitely, if erythema-producing doses are repeated at weekly intervals. Its counterpart in humans, known to Australian swimmers as "peeling," appears within a few days after an erythema-producing exposure and reaches a maximum after 7 to 10 days. If erythema-producing doses are repeated weekly, it also will continue indefinitely. Under these conditions, in both animals and man, the increased thickness of the stratum corneum constitutes a partial barrier to the passage of all wavelengths and the erythema-producing dose is definitely increased whether pigment is present or not.

Thus, it is clear that in any single subject of Type 1 (or an albino mouse) cornification will explain the degree of developed resistance occurring in that particular subject. However, some writers go further and assume that the difference in resistance between subjects of Type 1 and those of Type 2 is due to a corresponding variation in the cornifying ability of the types They make this assumption in order to reconcile the difference in resistance between Types 1 and 2 with their theory that erythema and skin cancer due to UVL depend on a photobiological reaction in the prickle-cell layer. They are forced to neglect the value of pigment, which is mainly beneath the prickle cells, and argue that the Malpighian layer is protected in subjects of Type 2 by a thicker stratum corneum than occurs in those of Type 1. This widely held point of view is epitomized in the following statement of Hall (1950): ". . . descendants of natives of the British Isles, particularly when blue-eyed, often exhibit an almost complete inability to acquire and retain a thick enough stratum corneum to protect them from rays of carcinogenic wavelengths in the amounts encountered in such regions as Texas, Arizona, Southern California and Australia."

There is, however, no evidence at all of such deficiency in the cornifying ability of subjects of Type 1, and we therefore made a direct investigation into the question. To do this, we required a fairly simple experimental method of determining relative degrees of thickness of the stratum corneum. Trials were made of several different ways of peeling and scraping the surface layer of the skin until the following procedure was evolved. It will be seen that the series reported also gives an indication of the degree of cornification occurring on exposed areas of average Sydney residents, under conditions of everyday life. Persons examined were chosen from hospital employees receiving approximately equal amounts of exposure. The only limiting factor in this regard is that subjects of Type 1 naturally tend to protect themselves from the sun more than do those of Type 2.

Experimental Details: Subjects were chosen on the basis of a clear line of demarcation between regularly exposed and covered skin so situated that specimens could be taken from the same aspect of the area concerned for both covered and exposed portions. This excluded possible regional variations in thickness of the stratum corneum. It was also necessary to choose a nonhairy region to avoid confusion of results from inclusion of hair particles.

For these reasons the side of the neck, above and below the collar, was found to be most convenient and satisfactory and was used in this series. The skin was cleaned with ether, and then on each section to be examined two parallel lines, 3.5 cm. apart, were drawn with a skin pencil. A blunt straight-edged scalpel was placed along one of the lines and then drawn across the skin (stretched with the fingers of the left hand) in a scraping fashion as far as the second line. The same blade, used by the same operator in all cases, was held at an angle of 45 degrees to the skin surface, and an even pressure was maintained. Ten strokes were made in one direction and ten in the opposite direction on each area. The direction of scraping was along the lines of skin flexure. All horny matter removed from each test area was transferred from the scalpel to a cigarette paper, in which it was folded and labeled. The papers were weighed separately, both containing the scale and without, on a balance accurate to the sixth decimal of a gram. The difference between these weights gave the weight of stratum corneum removed from each area. The disadvantage of the method is that all persons do not present a sharp line of demarcation between covered and exposed skin in

TABLE 1.—*Values for Subjects of Type One*

Case No.	Age	Sex	Occupation	Pigmentary Skin Type	Collagen Degeneration	Skin Cancer	Weight of Corneum Unit, 0.0001 Gm. Covered	Weight of Corneum Unit, 0.0001 Gm. Exposed	Increase in Weight of Corneum, 0.0001 Gm. *
1	48	M	Laborer	1	In exposed area tested	Keratoses elsewhere	150	202	52
2	38	M	Cook	1	In exposed area tested	Keratoses elsewhere	91	111	20
3	31	M	Doctor	1	No	No	76	142	66
4	40	M	Barber	1	In exposed area tested	Keratoses elsewhere	14	6	—8
5	21	M	Clerk	1	No	No	46	273	227
6	43	M	Driver	1	In exposed area tested	Keratoses elsewhere	28	28	0
7	29	M	Wardsman	1	No	No	1	84	83
8	32	M	Doctor	1	In exposed area tested	Previous keratoses	47	62	15
9	43	M	Chemist	1	In exposed area tested	Previous keratoses	32	54	22
10	30	M	Clerk	1	In exposed area tested	No	49	107	58
				Average values for patients of Type 1			53	107	54

* Weight of corneum unit when exposed to UVL minus weight of corneum unit when covered.

a nonhairy region on the side of the neck. The advantage is that it seems to be reasonably accurate, while not upsetting the patient to any degree. The results are given in Tables 1 and 2.

As can be seen, 20 men were selected, 10 being clearly of Type 1 and 10, of Type 2, while men of intermediate complexion were neglected.

Results: The tables were submitted to statistical assessment. The difference between means tested by the usual t-test gave a value of $t=4.47$, significant at the 0.1% level.

The figures show very clearly that there is definite, but variable, thickening of the stratum corneum in the exposed skin of residents of Sydney, under the conditions of everyday life. The variability is probably due to differing time intervals between the most recent heavy exposure to the sun and the day of testing. For example, a heavy exposure 10 days before the test would give a much higher value.

However, the most important fact arising from the investigation is that, contrary to general belief, persons of Type 1 actually cornify to a greater degree than those of Type 2 in response to regular solar exposure. This means that the protective action of the stratum corneum is greater in persons of Type 1 than in those of Type 2 for similar conditions of exposure. Thus, the dose of UVL received by the prickle-cell layer would be less in persons of Type 1. Even when, owing to the thicker stratum corneum, the actual amount of UVL entering the Malpighian layer is smaller, erythema is still more readily produced in persons of Type 1 than in those of Type 2. This obviously cannot be due to a direct effect of UVL upon the prickle cells. In persons of Type 2 almost the whole of the UVL reaching the pigmented basal layer is absorbed, whereas in persons of Type 1

TABLE 2.—*Values for Subjects of Type Two*

Case No.	Age	Sex	Occupation	Pigmentary Skin Type	Collagen Degeneration	Skin Cancer	Weight of Corneum Unit, 0.00001 Gm. Covered	Weight of Corneum Unit, 0.00001 Gm. Exposed	Increase in Weight of Corneum, 0.00001 Gm.*
11	41	M	Laborer	2	No	No	143	181	38
12	40	M	Doctor	2	No	No	76	25	—51
13	50	M	Clerk	2	No	No	60	84	24
14	36	M	Cook	2	No	No	2	16	14
15	44	M	X-ray technician	2	No	No	34	75	41
16	26	M	Wardsman	2	No	No	7	23	16
17	21	M	Male nurse	2	No	No	46	33	—13
18	33	M	Gardener	2	No	No	74	83	9
19	46	M	Doctor	2	No	No	21	23	2
20	27	M	Clerk	2	No	No	7	52	45
				Average values for patients of Type 2			47	60	13

* Weight of corneum unit when exposed to UVL minus weight of corneum unit when covered.

the small amount of pigment allows an appreciable fraction to enter the dermis. Although the amount of UVL penetrating the stratum corneum is less in persons of Type 1 than in persons of Type 2, the ultimate dosage reaching the dermis is greater. Thus we have a strong argument that the physiological response of erythema is due to the absorption of UVL in the cutis.

Peeling.—The question of "peeling" was discussed with many persons experienced in outdoor life, where exposure to the sun is frequent and its effects on the skin, well known. There was general agreement that peeling is directly proportional to the preceding erythema, being more marked in fair-skinned people than in dark. We have also observed that thickening of the stratum corneum does not last as long after the termination of exposure as does pigmentation. These facts would suggest that cornification is a simple consequence of dermal inflammation and that it is similar in nature to the peeling which follows erythema from fevers, exanthemata, or local inflammatory conditions, such as cellulitis or dermatitis. Thus, we believe that in the presence of solar erythema the dermis exercises a direct humoral influence upon the epidermis, producing increased cell division in the prickle-cell layer and a resultant increase in thickness of the stratum corneum. Minor degrees of horny thickening could be produced in the same way by subclinical erythema.

Penetration by UVL to the Dermis.—Having proposed that both erythema and cornification may be due to a direct action of UVL on the dermis, we proceed logically to consider whether the latter connective-tissue layer absorbs sufficient energy of UVL to produce significant biological effect. It is apparent that this energy, absorbed by the dermis, must be equal to that of the radiation transmitted through the epidermis, and we therefore made a review of reported work on penetration of UVL through the epidermis (Bachem and Reed, 1929, 1931; Lucas, 1931; Kirby-Smith, Blum, and Grady, 1942; Hardy and Muschenheim, 1934).

The estimation of the passage of UVL through the epidermis is fraught with many difficulties. Firstly, it is impossible to obtain sample layers of differing cellular thickness in exactly the same condition as during life. Secondly, the extreme degree of scattering of UVL produced by epidermis renders determination of the transmitted energy somewhat inexact. For these reasons, separate workers have used different types of specimens and a variety of methods to gauge the transmitted energy. The result is a fairly wide range of values. Nevertheless, a close examination of published results discloses two significant features.

All workers agree that, within the epidermis, the principal absorber of UVL is the region of nonviable cells above the prickle-cell layer and that, once UVL has passed this corneal region, the only real barrier to its progress is melanin. The experiments of Bachem and Reed, with differential thicknesses of epidermis, show that the percentage transmission through full-thickness epidermis (removed by blistering) is only slightly less than that through corneum and granulosa alone. In other words, the viable cells of the epidermis appear to absorb only a small percentage of the UVL, excepting when the basal layer is pigmented. Thus, in a person with little skin pigment, the energy of UVL reaching the dermis is not much less than that entering the prickle-cell region. Therefore, it follows that more energy of UVL is absorbed in the dermis than in the viable cells of the epidermis in a fair-skinned person, regardless of the degree of cornification. Furthermore, the energy absorbed in the dermis must be at least equal to that causing cornification, and therefore it must be biologically significant.

The next point to be extracted from the reports of these workers is the actual percentage of UVL (incident upon the skin)

that reaches the dermis. This value varies greatly, of course, with the thickness of the stratum corneum and the amount of pigment present. However, Blum (1940) has calculated that for normal facial epidermis, of 0.032 to 0.042 mm. thickness (but neglecting pigmentation), the proportion of UVL of 3000 A. penetrating to the dermis is between 20% to 72% of the incident rays. Longer wavelengths penetrate in increasing amounts. In a later paper (Kirby-Smith, Blum, and Grady, 1942) he reduces his estimate to 10% for untanned skin of the forearm and 1% to 2% for tanned skin. Thus, the true proportion is far from definite, probably through variability of skin samples and experimental difficulties. Nevertheless, it would appear that a significant percentage of UVL does reach the dermis in a person of Type 1, particularly when one considers the cumulative effect over a period of years in a typical Australian.

The weakness of cornification alone as a protector of the dermis now becomes apparent, since the maintenance of a thickened stratum corneum requires regular absorption of a certain amount of energy in viable cells of either the epidermis or the dermis, depending on the theory one favors. In either case, as the dermis absorbs more than the epidermis in a fair-skinned person, the dermis must receive a biologically significant dose of UVL. On the other hand, the combination of a slight increase in thickness of the stratum corneum (containing a small amount of pigment) with a marked increase of the melanin in the basal layer would reduce the dermal dose considerably, and this probably explains the resistance of the person of Type 2 to UVL.

Summary and Conclusions.—From the above physiological discussion we may draw several conclusions and a suggestion. Firstly, it seems clear that melanin is of importance in protecting the dermis from UVL. Secondly, it is equally clear that cornification alone is a poor protector. Thirdly, we are convinced that in many fair-skinned persons a biologically significant percentage of UVL does penetrate to the dermis. Fourthly, from our investigations, the fact emerges that, in general persons of Type 1 cornify more than those of Type 2 in response to solar exposure.

From the foregoing we have deduced that the only reasonable explanation of the physiological responses to UVL, which are more marked in fair-skinned persons, is that they are due to absorption of radiation in the dermis. Therefore, it is our suggestion that UVL causes a photobiological reaction in the region of the subpapillary vascular plexus producing firstly erythema and secondly a humoral influence. This influence stimulates cellular changes within the epidermis, which result in thickening of the stratum corneum. Pigmentation could be due to this influence but is more likely due to a direct action of UVL on the melanin-forming cells of the basal layer. Apart from this action UVL may have little primary effect in the epidermis.

Armed with this information we now turn to our main theme, which is consideration of a possible association between skin cancer and the connective tissue degeneration of the dermis occurring in areas exposed to the sun.

2. Source of Material

The patients used in the following investigations presented for treatment at a large skin clinic in Sydney (population 1,861,685; latitude 34 degrees S). The size of the clinic may be deduced from the fact that in the 12 months to Sept. 1, 1957, there were 3288 new patients attending, of whom 343 had squamous-cell carcinoma, and 35 had keratoacanthoma. These figures do not include the many old patients who returned with new lesions. Additional biopsy material used in this paper was obtained from other clinics within the same hospital.

3. Collagen Degeneration

Clinical Aspects.—It is well recognized that certain persons develop an atrophic change in the dermis in exposed areas, the resultant condition being known to dermatologists as "farmers' skin" or "sailors'

Fig. 2.—Moderately advanced collagen degeneration in a 29-year-old accountant of Type 1.

skin." Clinically it shows itself in the early stages, best on the forehead or sides of the neck, as a simple mottling of pinhead-sized, nonelevated yellowish areas in an otherwise normal skin. Later, the skin loses its elasticity; becomes thicker, with deeper furrows; shows irregular pigment spots, and may become erythematous. For reasons described later this condition will be referred to in our thesis as "collagen degeneration" of the skin.

Although much less investigational work has been reported on collagen degeneration than on skin cancer, it is extremely common, lending itself readily to observation. Its occurrence is found to parallel that of skin cancer to a remarkable degree. It is found only on the exposed areas, increasingly so with greater insulation, much more noticeably in fair persons than in dark (Eller and Eller, 1951), and frequently in association with skin cancer. In Australia we become used to seeing both these conditions, commonly in the 30- to 40-year-old group, not uncommonly in the 20- to 30-year-old group, and occasionally in even younger persons. Thus, neither condition can be termed "senile," as is commonly done in textbooks (e. g., "senile keratosis" and "senile elastosis"). Furthermore, from clinical experience and statistics, it seems clear that the time of onset is independent of age, being determined simply by the cumulative amount of exposure to UVL and the lack of protection in the patient's skin. Figures 2 through 4 show examples of different stages of collagen degeneration with and without skin cancer. Some of the

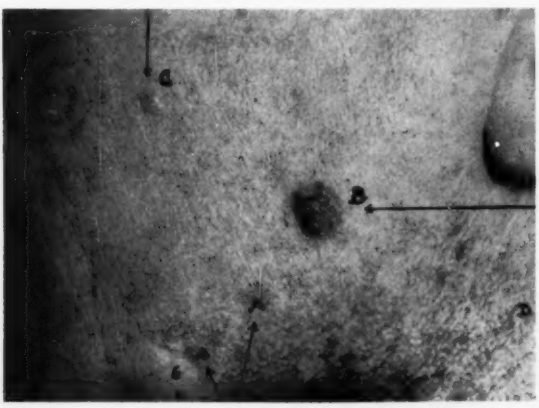


Fig. 3.—The cheek of a 72-year-old clerk of medium complexion, showing (*A*) solar keratoses, (*B*) early squamous-cell carcinoma, (*C*) pearly nodule of basal-cell carcinoma, (*D*) collagen degeneration, and (*E*) area of previous x-ray therapy.

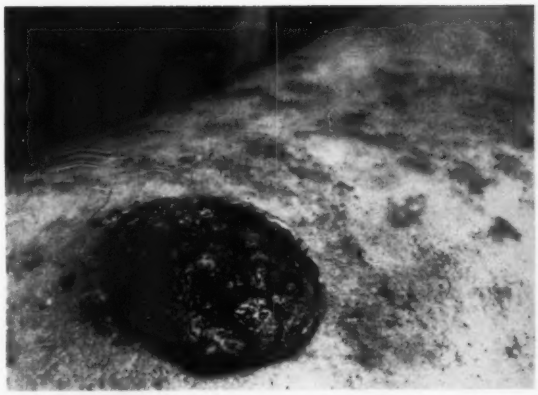


Fig. 4.—Squamous-cell carcinoma on the shoulder of 38-year-old laborer of Type 1.

illustrations are taken from young adults, and such pictures are readily available in this country.

We should like to point out that we agree with the division of the primary degenerative conditions of the dermis in exposed skin into the three separate entities of juvenile colloid milium, adult form of colloid milium, and collagen degeneration (Percival and Duthie, 1948). The first is a very rare condition having no association with our present discussion, although it occurs mostly in fair-skinned persons. The second is an uncommon condition and has no apparent association with skin cancer, although it may occur together with collagen degeneration (Fig. 5). It is the third division, variously referred to as senile elastosis and solar atrophy, which is our particular concern and which we prefer to call collagen degeneration.

Histological Aspects.—Collagen degeneration of the skin is an alteration in the structure of the subpapillary and papillary zones of the dermis. It commences around the subpapillary plexus of vessels and gradually extends into the papillary zone, until no normal collagen remains. It does not encroach upon the reticular layer to any appreciable extent.

Histologically the first sign of the lesion is the appearance of curled and twisted elastic fibrils around the subpapillary plexus (Fig. 6). These increase until they form a dense mat of slightly basophilic fibrils with a general arrangement that is more or less parallel to the skin surface. The staining reactions of these fibrils are

Fig. 5.—Acquired form of colloid milium, occurring with collagen degeneration, near the outer canthus of a 45-year-old farmer of medium complexion.

Fig. 6.—Man aged 36. Early stage of collagen degeneration in lower lip adjacent to a solar keratosis. Photomicrograph shows elastosis and ectasia of vessels in subpapillary plexus. Hematoxylin and eosin; × 150.

identical with those of elastic fibers, and for this reason the condition is usually designated "elastosis." The appearance of elastosis, however, is only transient, and a more appropriate term is collagen degeneration.

At first the fibrils stain more brilliantly than the surrounding collagen with hematoxylin and eosin stains, but as the lesion develops the elastotic mass acquires slight basophilia. At a late stage all fibrillary structure is lost, and there is then a mass of amorphous or homogeneous material which does not take any stain particularly well, though it may retain slight basophilia (Fig. 7).

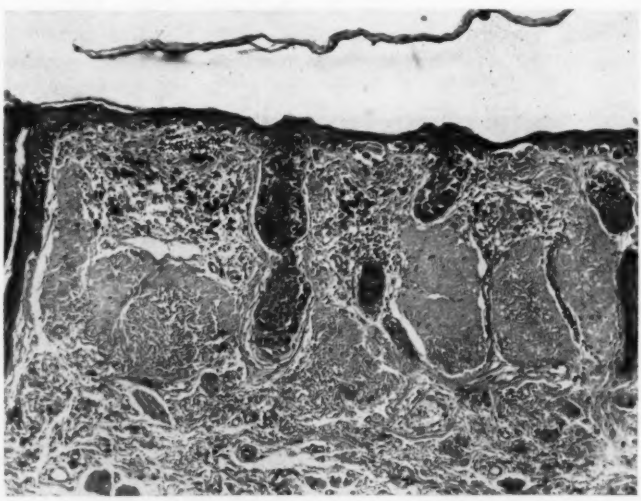


Fig. 7.—Woman aged 64. Cheek, showing junctional component adjacent to frankly invasive portion of lentigo maligna. There is advanced collagen degeneration with epidermal atrophy. Hematoxylin and eosin; × 35.

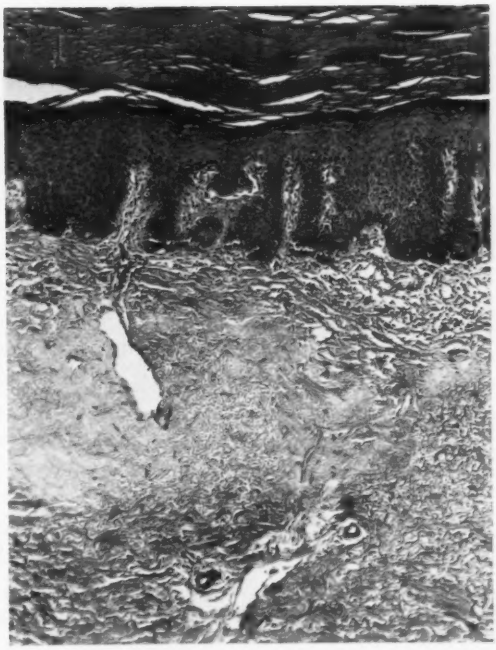


Fig. 8.—Man aged 35. Dorsum of hand adjacent to a squamous-cell carcinoma. Elastosis is becoming homogenized. Vessel within the area of collagen degeneration is ectatic. There is hyperkeratosis but no dyskeratosis. Hematoxylin and eosin; × 75.

Prior to the development of elastosis in some cases, but certainly by the time elastosis has developed, vessels of the subpapillary plexus into the papillary processes are unaffected until later in the evolution of the disorder (Fig. 8).

The homogenized material gradually replaces more and more of the papillary zone, and this is preceded or followed by ectasia of the vertical capillary loops. While the lesion is extending in this fashion, the epidermis often undergoes atrophy, losing its rete pegs and appendages. Finally, homogenized dermis extends from the subpapillary plexus to the basal layer of the epidermis, which by then has become

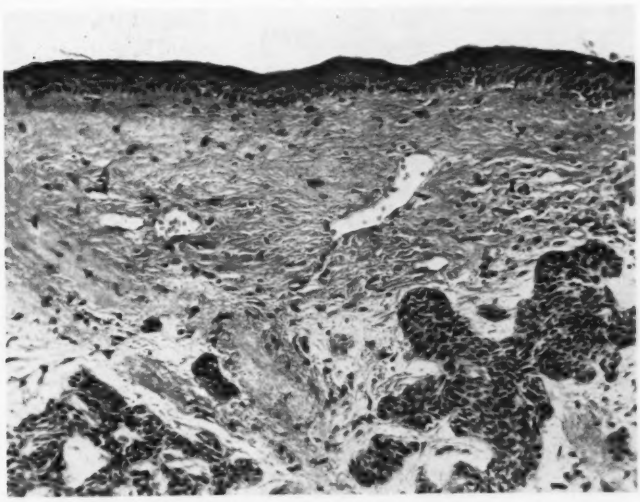


Fig. 9.—Woman aged 65. Basal-cell carcinoma of temple accompanied by advanced collagen degeneration. Note the resemblance to x-ray atrophy. Hematoxylin and eosin; × 75.

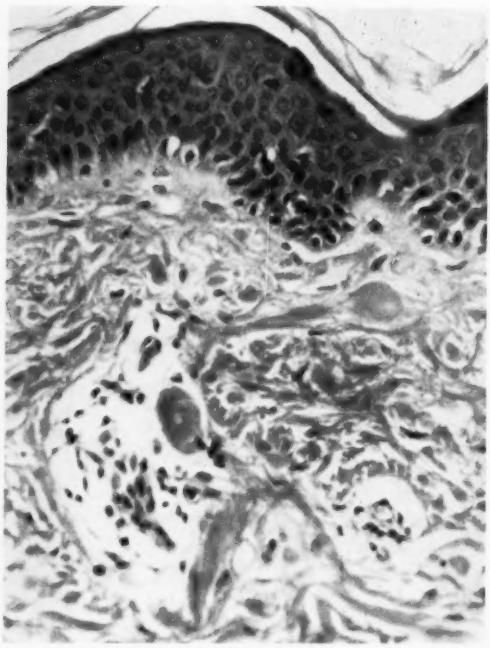


Fig. 10.—Woman aged 20. Early colloid degeneration in leg adjacent to a melanoblastoma. Hematoxylin and eosin; × 350.

atrophic. Vessels in the lesion are ectatic, and fibroblasts are prominent and in late stages atypical in appearance. Usually there is an increase in thickness of the horny layer of the epidermis, and often, an increase in pigmentation. In general, the appearances are very similar to those seen in chronic radiodermatitis (Fig. 9).

Collagen degeneration must not be confused with colloid degeneration. Whereas collagen degeneration commences around vessels of the subpapillary plexus, colloid degeneration is first seen in or just below the dermal papillae (Fig. 10). It takes the form of hyaline bubbles of eosinophilic material which gradually enlarge, replacing the

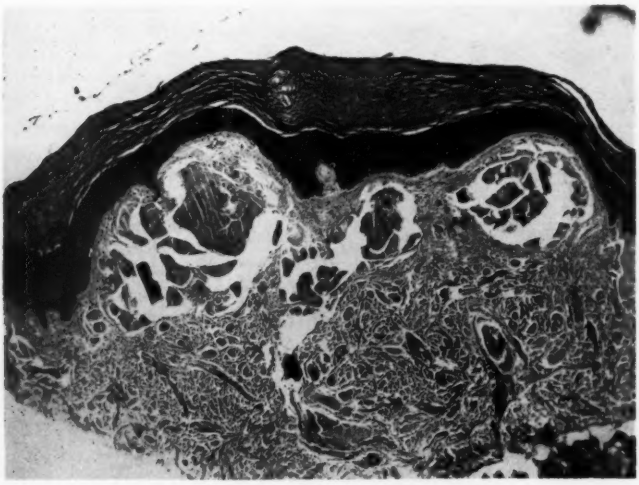


Fig. 11.—Man aged 27. Colloid degeneration in face. Masses of eosinophilic material display the characteristic "fractures." Hematoxylin and eosin; × 35.

collagen fibers of the papillary zone of the dermis. Plainly, it is the result of a change in the dermal ground substance (Fig. 11).

Pathogenesis.—In considering the pathogenesis of collagen degeneration we naturally think first of the fibroblasts. However, in all probability they play only a minor role in the early stages of the disorder, for, if they were to blame, we should expect the papillary zone of the dermis to be affected first rather than the subpapillary region. Alterations in the substrate, the ground substances, from which fibrils are formed, may well play a part in the genesis of the disorder. Certainly in the late stages of homogenization the appearances under the microscope suggest that there is then, at any rate, an alteration in the ground substance. In late stages, furthermore, fibroblasts gradually assume bizarre forms similar to though not as marked as those seen in x-irradiation effect.

The third possibility is that collagen is transformed into elastin. That collagen can be converted into elastin has been amply demonstrated in vitro by Keech et al. (1956). By treating collagen with various agents, physical and chemical, elastin networks were manufactured. They found that irradiation by ultraviolet light at 29 C could bring about this conversion. The view that the fibrils in collagen degeneration are actually composed of elastin has been confirmed by the work of Lansing (1955), who showed that incubating a portion of skin exhibiting elastosis with elastase dissolves and removes the elastic elements therein.

That collagen degeneration is due to UVL is shown by its geographical and anatomical occurrence, its increasing incidence both in fair-skinned persons and with greater solar exposure, and its parallel in these features to skin cancer.

That it is a direct effect on the dermis depends on our demonstration that in subjects of Type 1, the susceptible persons, a significant amount of UVL does reach the dermis, while in those of Type 2, the resistant persons, very little does so. Indeed, the only explanation of the protective action of pigment is, as in the case of erythema, that collagen degeneration is due to UVL which actually reaches the dermis.

The histological changes of collagen degeneration are first seen about the vessels of the subpapillary plexus and later spread up into the papillae. If we supposed that collagen degeneration were due to toxic substances permeating from the epidermis, we should expect the histological changes to proceed in the reverse direction.

Because the vessels of the subpapillary zone lie parallel to the skin surface, they are vulnerable to any ultraviolet light penetrating to that depth. The vertical loops, though approaching closer to the skin surface, present a smaller target. As a consequence, ectasia is seen first in the subpapillary plexus, and only at a later stage are the vertical loops affected. Collagen degeneration starts around the vessels of the subpapillary plexus, and later it gradually spreads up into the papillary zone, eventually replacing all normal collagen. These facts suggest that the effect of ultraviolet light on the blood vessels is to impair the metabolism of the surrounding connective tissue. This is probably accomplished by a change in the ground substance. Whether elastin fibrils are manufactured from the abnormal ground substance *de novo* or whether in its presence collagen becomes transformed into elastin has not been determined. Whatever the mechanism, elastosis is only a phase in the evolution of the disorder. In the final stage fibroblasts are manifestly atypical and the production of fibrils has ceased.

Summary.—Our concept of collagen degeneration is that of a progressive degradation of the structure of the subpapillary and papillary zones of the dermis due to excessive exposure to UVL. At first collagen in the region of the subpapillary plexus of vessels is replaced by elastic fibrils, with progressive encroachment on the papillary zone of the dermis. Gradually

the affected area becomes homogenized, and the overlying epidermis may undergo atrophy. These phenomena are, in our opinion, due to altered tissue metabolism originating from injury to the dermal vessels by ultraviolet light.

4. Solar Keratosis

Clinical Aspects.—Solar keratosis is a precancerous condition, found only on exposed portions of the body, and it is generally accepted that UVL is the actual cause. This belief is strongly backed by the geographical occurrence of keratoses and by animal experiments in which it has been shown that wavelengths between 2900 A. (the lower limit of solar radiation) and 3200 A. will produce cutaneous malignancy readily (Rusch, Kline, and Baumann, 1941; Blum, 1948).

Definite information is available about the person who is most susceptible to solar keratosis, and these data hold equally well in relation to basal-cell carcinoma and squamous-cell carcinoma. Clinical experience, backed by case statistics, shows that the less the amount of pigment in his skin the greater is a person's tendency to develop these forms of skin cancer (Paul, 1918; Molesworth, 1944; Ward, 1952; Belisario, 1954; Hall, 1950; Lancaster, 1956; Lancaster and Nelson, 1957; Elliott and Welton, 1946). Thus, it is definite that persons of Type 1 are susceptible to their development while those of Type 2 are resistant.

There are three reasons why statistics do not show the much greater susceptibility of persons of Type 1. Firstly, case series generally list only patients and not the number of lesions. This gives rise to an obvious fallacy, because, in practice, patients of Type 1 are commonly treated for 10 lesions (especially keratoses) at one sitting; intermediate types, for 2 or 3, and the occasional patient of Type 2, for 1. Thus, if the actual number of lesions were listed, instead of the number of patients, the true picture would be more easily seen. Secondly, it is obvious that most patients of Type 1 tend to protect themselves from the sun, while those of Type 2 revel in it. The result is that the fairer members of the population suffer less solar exposure than their more pigmented fellows, and the resultant error in skin cancer statistics cannot be corrected. Thirdly, if the age of onset were listed, it would be found that fair-skinned persons develop lesions at a much earlier age than the darker types.

A further significant aspect of solar keratosis is its frequent association with obvious collagen degeneration (Fig. 3). For the purposes of this paper, 200 consecutive patients with a diagnosis of solar keratosis were examined clinically for evidence of this second abnormality. The series covered various age groups (from 22 to 86), social strata, and types of occupation. The result was that, in every case, clinical signs of collagen degeneration were visible either in the immediate vicinity of the lesion or in another exposed area. This finding stimulated us to an extensive histologic survey of the dermis in cases of solar keratosis.

Histological Aspects.—A solar keratosis has an epidermal component and a dermal component. The affected portion of the epidermis is dyskeratotic and has no granular layer, and so there is a thick parakeratotic surface. The cells surrounding the orifices of sweat ducts and pilosebaceous follicles do not participate in this dyskeratosis, and, as a result, the keratinous layer overlying and plugging them is normal in type. Often the cells of the Malpighian layer in solar keratoses have dark, clumped nuclear chromatin which is highly reminiscent of Bowen's disease, and, as in Bowen's disease, there is an abrupt transition between epidermis of normal type and the abnormal epidermis of a solar keratosis (Fig. 12).

In the dermis there is always advanced collagen degeneration and always some degree of inflammatory-cell infiltration. The inflammatory infiltrate is composed of lymphocytes and their precursors. Seldom very dense, it is confined to the papillary

Fig. 12.—Woman aged 64. A solar keratosis from dorsum of the hand. The characteristic collagen degeneration, vascular ectasia, chronic inflammation, and dyskeratosis are well shown. Cells of a sweat duct do not participate, although there is hyperkeratosis. Hematoxylin and eosin; × 75.

zone of the dermis and is usually little more than a mantling of the vertical capillaries.

In the seven years ending June, 1957, we examined 643 biopsy specimens of solar keratosis. Among these were 28 lesions from persons below the age of 40 years. This figure represents 4.4% of the total figure and is comparable to the figure for squamous-cell carcinoma, which was 4.6% for persons aged less than 40 years. The youngest was a young woman aged 25 years, with a keratosis of the cheek. There were two other women in the under-40 age group, one aged 35 years, with a lesion on the lower lip, and the other aged 39 years, in whose case the site was not stated.

The sites of lesions in this group under the age of 40 years were as follows: lower lip, 16; cheek, 2; eyelid, 1; ear, 1; dorsum of hand, 5; unknown site, 3.

The significant feature is, of course, the vulnerability of both the lip and the dorsum of the hand. The lip has a very thin epithelial layer and contains no pigment. The dorsum of the hand is covered by thin epithelium, and in outdoor workers it is constantly exposed to the sun.

Pathogenesis.—We have shown that a solar keratosis is a dyskeratotic lesion due to an aberration in the basal-cell layer of the epidermis and is invariably associated with collagen degeneration of the dermis and a mild inflammatory reaction. We believe that the changes in the epidermis are caused by those in the dermis for the following reasons:

1. We have shown that collagen degeneration is almost certainly due to the direct action of UVL on the dermis in the region of the subpapillary plexus.

2. We have also shown that the only significant anatomical difference between Type 1 and Type 2 skins is the presence of pigment in the basal layer of the latter. The result of this difference is that, while the epidermal dose of UVL is approximately equal in the two types, the energy absorbed by the dermis is much greater in Type 1 than in Type 2. Thus, the only reasonable explanation for the much greater

incidence of solar keratoses in persons of Type 1 is that the effect of UVL is mediated by its action on the dermis. The fact that the epidermal dose is approximately equal in persons of Type 1 and those of Type 2 is strongly against the theory that keratosis is caused by the primary effect of UVL on the epidermis.

3. If solar keratosis and collagen degeneration were simply coincidental one would expect the keratosis to precede the dermal changes in at least some (perhaps half) of the cases.

4. The epidermal atrophy found in well-developed, but uncomplicated, collagen degeneration suggests a profound disturbance of its nutrition. At the same time, it is clear that the cellular environment of the epidermis is wholly dependent on interchanges with the underlying dermis, and a degenerative condition in it would be expected to produce gross metabolic disturbances in the epidermis.

Having developed this theory of the mode of action of UVL in the pathogenesis of solar keratoses, we found the interesting and supporting paper of Engman (1925).

The actual mechanism by which a solar keratosis develops probably depends upon the superimposition of a mild chronic dermatitis, either solar or traumatic in origin, on preexisting collagen degeneration. Whereas inflammation alone constantly produces acanthosis, inflammation in the presence of collagen degeneration produces dyskeratosis. We believe that the difference in reaction is due to impairment of nutrition of the epidermis.

The pilosebaceous follicles and sweat duct orifices are less often affected, probably for the reason that their nutrition depends more upon zones of the dermis deep to the collagen degeneration. This is reflected by the sudden change to cells of normal type near the orifices of these appendages (Fig. 12).

There is often a close resemblance between Bowen's disease and very dyskeratotic examples of solar keratosis and so differentiation on pattern alone may be difficult unless one recollects that solar keratoses are invariably associated with collagen degeneration, whereas Bowen's disease is not.

Summary.—A solar keratosis is a localized dyskeratosis resulting from the effect upon the epidermis of a mild chronic der-

Fig. 13.—Keratoacanthoma on upper lip of elderly woman. Collagen degeneration of mild degree is present.

TABLE 3.—*Site and Age Incidence of Keratoacanthoma*

Site	Age, Yr.														Totals	
	21–30		31–40		41–50		51–60		61–70		71–80		81–90			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Head and neck	1		9	1	5	1	3	4	10	6	3	14	6	2	37	28
Trunk							1		1						2	
Hand and fingers	1		2		5	1	4	4	11	7	2	1	3		28	13
Wrist and forearm			2		1		6	2	3	4	5	5	1		18	11
Leg								3								3
Foot										1						1
Totals	2		13	1	11	2	14	13	25	18	10	20	10	2	85	56
															141	

matitis in the presence of collagen degeneration of the dermis.

5. Keratoacanthoma

Clinical Aspects.—Keratoacanthoma (Fig. 13) is a self-healing hyperplastic epidermal lesion which has become more widely recognized in recent years since the publication of papers such as those by Finley (1954) and Fouracres and Whittick (1953). It is seldom seen elsewhere than on exposed skin and is commoner with advancing years. Furthermore, our own clinical impressions, backed by those of Dr. J. C. Belisario and Dr. A. G. Finley (personal communications), is that fair-skinned persons are more susceptible to the development of this condition than are dark-skinned types. Therefore, we believe, as do Belisario and Finley, that long-term exposure to sunlight is a factor predisposing to the onset of keratoacanthoma and that the presence of cutaneous pigment acts to some degree as a protective agent.

In a series of 141 examples in which sufficient tissue was removed to make a diagnosis, the lesions were found to occur predominantly in the older age groups and were commonest on the exposed parts of the body (Table 3).

Histological Aspects.—Of the 141 specimens listed in Table 3, there was insufficient tissue for the determination of the presence or absence of collagen degeneration in 31. In the remaining 110, collagen degeneration was present in all but 11.

Histologically it was found that a keratoacanthoma, as well as causing a nodule on the surface, pushes down into the dermis in a characteristic pattern, indenting rather than invading it (Fig. 14).

There is always an inflammatory reaction present. Sometimes it is very dense and contains numerous polymorphonuclear

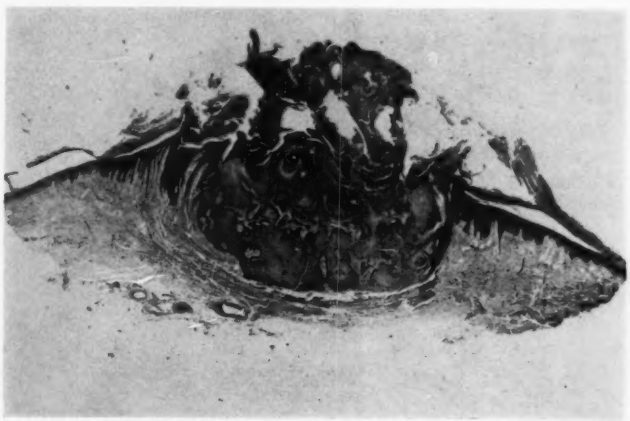


Fig. 14.—Man aged 64. Keratoacanthoma from dorsum of hand. Hematoxylin and eosin; × 8.

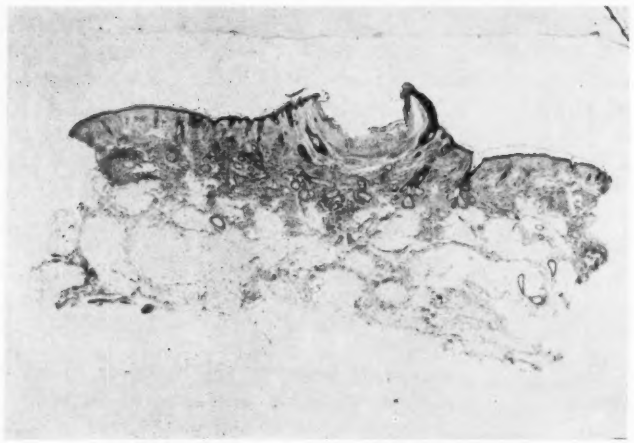


Fig. 15.—Woman aged 50. Bed of a keratoacanthoma from cheek, near nose. Involution had commenced, and degenerate epithelium was detached from the specimen in preparation. Hematoxylin and eosin; × 4.

leukocytes which even penetrate amongst the cells of the epithelial masses. Even when the inflammatory reaction is not such a prominent feature, it is still much greater than that usually seen in a dermatitis or the solar keratosis.

In due course the inflammatory reaction subsides, and then the keratoacanthoma ceases to grow. The cells at the periphery of the epithelial masses lose their viability and come to resemble the nonviable differentiating cells which they enclose. A foreign-body reaction destroys this inert mass, and eventually a cicatrix is all that remains (Figs. 15 and 16).

Pathogenesis.—It is well known that chronic inflammatory lesions in the skin cause proliferation of the overlying epithelium which may attain pseudoepitheliomatous proportions. In a few of our examples of keratoacanthoma the epithelial proliferation seems to have resulted from the presence of inflammation alone. In others the epithelial hyperplasia was far beyond that which could be expected to result from the modest degree of inflammatory infiltrate which was present. In these, there was always some degree of collagen degeneration in addition. Keratoacanthoma can thus be regarded as the result,

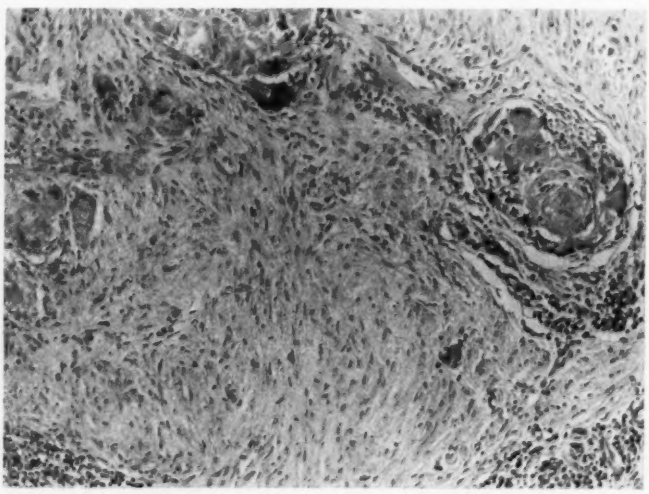


Fig. 16.—Base of lesion illustrated in Figure 15. Foreign-body reaction around degenerating epithelium. Hematoxylin and eosin; × 175.

in most cases, of a fairly severe inflammation in the skin of a person already afflicted with collagen degeneration of the dermis. Initially there is an acute inflammatory exudate which later changes to one of chronic type. At one end of the scale there is minimal inflammation with prominent collagen degeneration, while at the other, inflammation alone accompanies the lesion. Once the inflammation subsides the stimulus to epithelial hyperplasia diminishes until it can no longer maintain the lesion, which then regresses, and the epithelial masses degenerate to the status of foreign body. Except for a few examples of keratoacanthoma resulting from inflammation alone, the presence of collagen degeneration appears to intensify the epithelium-stimulating effect of inflammation.

Summary.—Keratoacanthoma is a pseudoepitheliomatous hyperplasia in response to inflammation which is intensified by the presence of collagen degeneration. As a result of this, it is found predominantly on the exposed parts of the body of fair-skinned persons.

6. Squamous-Cell Carcinoma

Clinical Aspects.—Squamous-cell carcinoma of the skin occurs on the same areas, in the same age groups, and with the same relationship to cutaneous pigment as solar keratosis. The commonest factor in its causation in Australia is repeated exposure to UVL over a period of years. Other influences which may cause its appearance are smoking (in cancer of the lip), arsenic, tar, chronic infections such as varicose ulcer, and old scars caused by burns or radiotherapy.

To assess the frequency of clinical association of the solar type of squamous-cell carcinoma with collagen degeneration, 36 consecutive patients were examined. Two seen intercurrently were neglected, as they were obviously not of solar origin, one having arisen on a varicose ulcer and the other being at the angle of the mouth, in association with buccal leukoplakia, in a heavy smoker.

As with solar keratosis, in every case of squamous-cell carcinoma of solar origin there was evidence of collagen degeneration, either in the vicinity of the tumor or in another exposed area (Figs. 3 and 4). The ages of the patients ranged from 31 to 75. These observations led us to a detailed histological analysis of a much larger series.

In the year ending June 30, 1957, there were 209 biopsy specimens of squamous-cell carcinoma for which adequate data concerning age, sex, and site of the lesion were supplied. These are classified in Table 4.

From Table 4 it is clear that the exposed parts of the body are most frequently affected by squamous-cell carcinoma. The incidence of squamous-cell carcinoma in outdoor workers is high, and, because few women are outdoor workers, the female incidence is comparatively low. The age incidence follows the pattern of most forms of cancer, being highest in the later decades, although there is always an apparent falling off after the age of 70, because of the fewer persons surviving in those age groups.

Histological Aspects.—In Table 5 the incidence of collagen degeneration has been analyzed. Some specimens were rejected

TABLE 4.—*Incidence of Squamous-Cell Carcinoma*

Site	Age, Yr.																Totals	
	21–30		31–40		41–50		51–60		61–70		71–80		81–90		91–100			
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Head and neck	2		8	2	25	2	20	3	37	5	34	7	3	6		1	129	26
Upper limb			1		3	1	9	3	16	3	7	1	1		1		38	8
Trunk			1		1												2	
Lower limb						3			2			1					2	4
Totals	2		10	2	29	6	29	6	55	8	41	9	4	6	1	1	171	38

TABLE 5.—*Distribution of Squamous-Cell Carcinoma With and Without Collagen Degeneration Among 130 Patients Seen in Twelve Months*

Site	With Collagen Degeneration, No.	Without Collagen Degeneration, No.
Head and neck		
Lip	32	0
Ear	19	0
Face	12	4
Nose	6	2
Forehead	4	0
Temple and scalp	4	1
Neck	3	0
Upper limb		
Dorsum of hand	25	1
Wrist	2	0
Forearm	6	0
Shoulder	0	1
Chest	1	0
Lower limb		
Leg	3	1
Foot	0	3
	117	13

because of x-irradiation effects; some, because the cautery had coagulated the specimen, and others, because the specimen was not large enough for the determination of the presence or absence of collagen degeneration.

Histologically, every squamous-cell carcinoma associated with collagen degeneration gave clear evidence that it had commenced in a solar keratosis.

The analysis in Table 5 points clearly to the high incidence of squamous-cell carcinoma in the exposed parts of the body. Although most of the lesions were accompanied by collagen degeneration, a few caused by carcinogens other than ultraviolet light would be expected. This would account for lesions on the unexposed parts of the body and the small proportion in the exposed areas which were not associated with any obvious dermal change.

Pathogenesis.—If we restrict our consideration of pathogenesis to the solar form of squamous-cell carcinoma, the discussion and conclusion are exactly the same as already given for solar keratosis. Again, we believe that the undoubtedly greater incidence of this type of cancer in persons of Type 1 can be explained only by the acceptance of the dermis as the mediator of the carcinogenic action of UVL. It is interesting to reflect that another cause of squamous-cell carcinoma, namely, x-radiation, which has an obviously direct effect on the dermis, causes a histological appearance similar to that described above as collagen degeneration.

In the analysis in Table 5 it can be seen that the lip and the dorsum of the hand are very commonly affected by squamous-cell carcinoma. The lip has very thin epithelium and contains no melanin. To these features its vulnerability may be ascribed. Furthermore, no carcinoma of the lip has been unaccompanied by collagen degeneration. These facts suggest that collagen degeneration plays a leading role in the genesis of carcinoma of the lip.

Carcinoma of the dorsum of the hand, as in the lip, rarely occurs in the absence of collagen degeneration, but an interesting comparison can be made between the age incidences of carcinoma in these two sites. Using the large series of 1316 examples of squamous-cell carcinoma histologically examined in the seven years ending in June, 1957, we found that 61 (4.6%) occurred in persons under the age of 40 years. This is in accord with the age incidence of solar keratosis. Of 201 patients with carcinoma of the lip, 18 (9%) were under the age of 40 years, whereas for the dorsum of the hand only 3 (1%) of 271 were under the age of 40 years.

The lip, then, is not only very commonly attacked by squamous-cell carcinoma, but carcinoma occurs there at an earlier age than in other sites. This can be ascribed to the absence of pigmentation and the greater facility, therefore, with which collagen degeneration is produced.

Only a small proportion of solar keratoses become malignant, but so common are these lesions in Australia that the figures for squamous-cell carcinoma are very high. The acutal mechanism by which malignant transformation of a keratosis occurs is not clear. The keratinous layer on the surface of an established keratosis is too thick to permit the passage of much additional UVL, and so other factors must be con-

sidered. The likeliest is a mutation arising out of the continued nutritional disturbance due to the presence of collagen degeneration. This mechanism may also apply to carcinoma arising in long-standing x-irradiation effect.

Summary.—Squamous-cell carcinoma of the skin in Australia is a very common condition. It arises, in most cases, by the transformation of a solar keratosis. In our opinion the carcinogenic effect of ultraviolet light is mediated by its action on the dermis.

7. Basal-Cell Carcinoma

Clinical Aspects.—The general facts of age incidence and of relationship to solar exposure and pigmentary type are the same in basal-cell carcinoma as in solar keratosis. There are, however, certain notable differences in other aspects of their occurrence. Firstly, basal-cell carcinoma is rare on the backs of the hands and forearms and is never found on the lips. It occurs predominantly on the exposed portions of the head and neck. Secondly, a small percentage of cases occurs on areas which have seen little or no sun (e. g., the trunk and lower limbs). Thirdly, a further small percentage of cases appears to have a definite nevoid association and may be accompanied by other inherited abnormalities (e. g., the cases described by Ward, 1957). This point, together with the anatomical distribution of lesions in areas well supplied with pilosebaceous follicles, suggests the possibility that a basal-cell carcinoma is an aberrant attempt to form a hair follicle. Finally, as with squamous-cell carcinoma, occasional cases are seen with a history which indicates a specific carcinogen, such as arsenic or tar.

Setting the last-mentioned instance aside, we are left with two main groups. By far the largest group consists of the lesions occurring in light-exposed skin and obviously due to solar radiation. The second group, a small minority in our clinic and not of solar origin, includes lesions on covered skin of unknown cause (e. g., multiple superficial lesions of the trunk) and lesions of nevoid type. The nevoid lesions are mostly small multiple nodules on the head and neck and they may occasionally occur in persons of Type 2 without excessive solar exposure. Between these definite nevoid cases and the obvious solar ones, there appears to be a no man's land of cases of mixed origin. In these patients we presume a nevoid diathesis which has been accelerated by the action of UVL. Thus, by varying combinations of the inherent tendency of the patient, his pigmentary type, and his cumulative exposure to the sun, we get the endless variety of clinical presentations so well known in this condition.

To make a clinical judgment of the association between basal-cell carcinoma and collagen degeneration, we examined 110 consecutive patients with basal-cell carcinoma. Three had multiple superficial lesions, which in one followed the administration of an arsenical for psoriasis; these were rejected as having no solar association. Only two of the remaining patients showed no sign of collagen degeneration, both being of the intermediate complexion type, one a male and one a female. The former had a single lesion on the lower eyelid, and the latter had two small rounded lesions on the chin with a 10-year history. Both cases were taken to be of the nevoid type. Three patients (all men aged more than 50 years) each had multiple (up to 10) small rounded nevoid-type lesions on the face associated with frank collagen degeneration. Each of the remaining 102 patients had lesions on an exposed area and showed collagen degeneration either in the vicinity of the lesion or in another exposed area.

In our clinic, biopsies are performed in basal-cell carcinoma only when there is any doubt of the diagnosis, with the result that approximately 1 in every 10 lesions is submitted to histological examination. Obviously, such atypical cases will show a

TABLE 6.—*General Incidence of 185 Examples of Basal-Cell Carcinoma*

	Age, Yr.																	
	11–20		21–30		31–40		41–50		51–60		61–70		71–80		81–90		Totals	
Site	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Head and neck		1	5	1	5	7	13	6	18	6	37	10	22	14	5		105	45
Upper limb			1				2		2	1	4		2	1		1	11	3
Trunk			1		1	1		3	2	1	1		1				6	5
Lower limb					1	1	2			2	2			2			5	5
Totals		1	7	1	7	9	17	9	22	10	44	10	25	17	5	1	127	58

greater percentage of nevoid types than the above clinical series, because the definite solar lesions, being more easily diagnosed with the naked eye, are less often submitted to biopsy.

Histological Aspects.—In analyzing our data concerning basal-cell carcinoma it has been necessary in the case of patients with multiple tumors to classify only the regions affected and not the number of tumors or the number of patients. Therefore, a patient with two lesions on the face becomes a single entry, but in the case of a tumor at another site, such as the leg, as well as one on the face, we have classified both regions.

Following the course outlined above, we have classified the biopsy specimens received from several clinics in the one hospital, in the 12-month period ending June 30, 1957. They numbered 242, but we rejected 20 because there were insufficient data concerning age, sex, and site. Another 37 have been rejected because the specimens were not large enough for us to determine whether collagen degeneration was present or absent. This left 185 examples of basal-cell carcinoma for analysis.

The general grouping of the specimens according to age and sex of the patient, together with site of the lesion, is given in Table 6.

It is obvious that there is an increasing incidence of basal-cell carcinoma with age in the exposed parts of the body. The youngest patient was a woman of 18 years, who presented with a lesion on the cheek unaccompanied by collagen degeneration. The youngest patient with collagen degeneration in this series was a man of 23 years, who presented with a rodent ulcer on the cheek. We have, however, seen advanced collagen degeneration accompanying a basal-cell carcinoma in a youth aged 18 years (not in this series).

Whereas the incidence of basal-cell carcinoma of the head and neck increases with age (making allowances for the fewer persons in the last two decades), that in the unexposed portions does not increase. This fact suggests that the cumulative effect of solar radiation has played an important part in producing the lesion on the head and neck.

Table 7 gives the incidence of collagen degeneration in relation to site of the lesion.

From Table 7 it can be seen that collagen degeneration accompanies most of the lesions occurring in exposed parts of the body. The lesions of the upper limb were mainly on the forearm, wrist, and hand, and the solitary lesion of the trunk was in the interscapular area. Of the 37 lesions excluded because the specimens were inadequate for determination of the presence or absence of collagen degeneration, 35 were from exposed areas of the body. In all probability most of these would have proved positive had sufficient tissue been removed.

The typical lesion was accompanied by severe collagen degeneration, which in most

TABLE 7.—*Incidence of Collagen Degeneration in Persons with Basal-Cell Carcinoma*

	With Collagen Degeneration		Without Collagen Degeneration	
Site	M	F	M	F
Head and neck	92	41	13	4
Upper limb	7	2	4	1
Trunk	1	0	5	5
Lower limb	0	0	5	5
	100	43	27	15

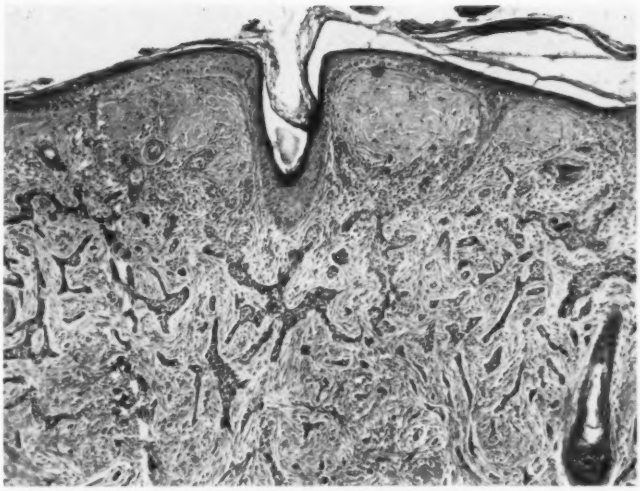


Fig. 17.—Woman aged 69. Morpheic type of basal-cell carcinoma of forehead. Advanced collagen degeneration with epidermal atrophy overlying a cicatrizing basal-cell carcinoma. Hematoxylin and eosin; ×35.

cases showed fairly advanced homogenization (Fig. 17).

From Table 8 it can be seen that the incidence of basal-cell carcinoma without collagen degeneration shows a fairly uniform distribution throughout all age groups, but the figures are insufficient for any definite conclusions.

TABLE 8.—*Incidence and Site of Basal-Cell Carcinoma Unaccompanied by Collagen Degeneration*

	Age, Yr.																Totals	
	11–20		21–30		31–40		41–50		51–60		61–70		71–80		81–90			
Site	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
Head and neck		1	1		1	1	1		3	1	1		4	1	2		13	4
Upper limb			1						2				1			1	4	1
Trunk			1		1	1		3	2	1			1				5	5
Lower limb					1	1	2			2	2			2			5	5
Totals		1	3		3	3	3	3	7	4	3		6	3	2	1	27	15

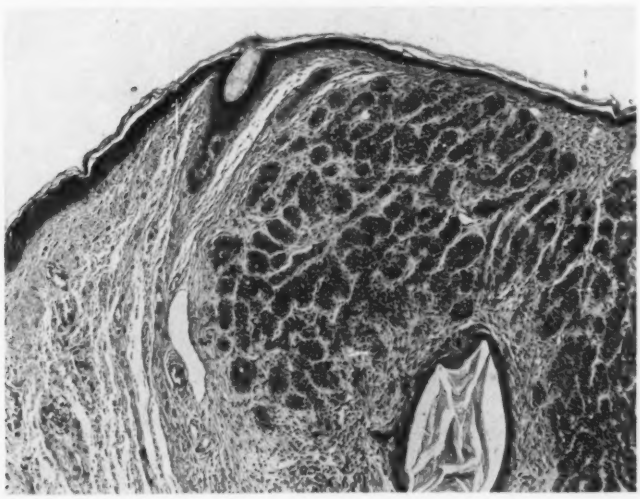


Fig. 18.—Woman aged 58. Nevoid type of basal-cell carcinoma of face. Hematoxylin and eosin; ×35.

Fig. 19.—Man aged 27. Epithelioma adenoides cysticum of chest, showing hair follicle formation. Hematoxylin and eosin; × 75.

Although the obvious hamartomatous lesions of the epithelioma adenoides cysticum type have been excluded, there are still in this series many tumors which present an organoid appearance and may well be nevoid (Fig. 18). These were often unaccompanied by collagen degeneration. One was a pigmented basal-cell carcinoma in the hairy part of the scalp of a dark-skinned Levantine doctor. Tumors unaccompanied by collagen degeneration were commoner on the head and neck than elsewhere, and the higher incidence suggests that an inherent tendency was perhaps hastened by

Fig. 20.—Man aged 26. One of numerous lesions of epithelioma adenoides cysticum type from chest. Illustrates attempts at formation of pilosebaceous follicles. Hematoxylin and eosin; × 75.

solar radiation; although no obvious histological evidence for such a view can be presented.

Pathogenesis.—There is a growing belief that basal-cell carcinoma represents a latent nevoid condition, that it is in reality an aberrant attempt at forming a pilosebaceous follicle. This concept implies that the "basal cells" are differentiated cells homologous with those of the hair matrix. This would explain the relatively benign course of the lesion, its occurrence only in the hair-bearing portions of the skin, and the occasional differentiation to sebaceous glands. At one end of the scale is the obviously hamartomatous epithelioma adenoides cysticum, which may actually contain recognizable pilosebaceous follicles (Figs. 19 and 20). At the other end of the scale is the undifferentiated basal-cell carcinoma of classical appearance.

Further evidence to support the nevoid character of these lesions is to be found in the age incidence compared with the age incidence of patients exhibiting solar keratoses and squamous-cell carcinomas.

In the seven-year period to July, 1957, biopsy specimens of 1678 examples of basal-cell carcinoma were examined. Of these, 118 (7.6%) were from persons under the age of 40 years. In the same period 643 solar keratoses and 1316 examples of squamous-cell carcinoma of skin were examined, and, of these, 28 (4.4%) and 61 (4.6%), respectively, were from persons under the age of 40 years. The figures for solar keratosis and squamous-cell carcinoma correspond, but for basal-cell carcinoma there is a higher percentage of young persons. This suggests that there is a greater inherent tendency to produce a basal-cell carcinoma than other forms of skin cancer. This supports our hypothesis that there is a nevoid background to basal-cell carcinoma.

In patients with basal-cell carcinoma, collagen degeneration was present in a significant number. To some it may appear that collagen degeneration accompanying basal-cell carcinoma of the exposed parts of the body is merely an indicator of the amount of solar radiation received by the patient. If, indeed, collagen degeneration plays no etiological role, one would expect basal-cell carcinoma of the exposed parts of the body to occur in young persons more frequently without collagen degeneration. Yet, of 85 basal-cell carcinomas of the head and neck of persons under the age of 40 years, 68 were accompanied by collagen degeneration (July, 1950, to June, 1957). Basal-cell carcinoma with collagen degeneration has an earlier incidence than the other hyperplastic conditions of the skin which follow collagen degeneration.

From these observations it seems that collagen degeneration which we know to be due to solar radiation must play an important part in the genesis of basal-cell carcinoma as it does in solar keratosis and squamous-cell carcinoma.

Summary.—We regard basal-cell carcinoma as a nevoid condition either overt or latent, so that some tumors arise spontaneously and others, only after varying degrees of enviromental stimulation. The environmental factor is mainly ultraviolet light, and its action in accelerating and intensifying the tendencies already present is, we believe, mediated through its effect upon the dermis.

8. General Summary

We have made a systematic review and investigation of the physiological and pathological effects of ultraviolet light (UVL) on the skin.

For the sake of convenient description, Europeans were divided into two main types, depending on the pigmentary content of their skin, Type 1 being fair-skinned and Type 2, dark-skinned. The merits of pigmentation and cornification as protectors against UVL are discussed. A method of investigating relative degrees of thickness of the stratum corneum is described, and it is proven that in general persons of Type 1 cornify more than those of Type 2 in

response to solar exposure. It becomes apparent that variations in thickness of the statum corneum do not explain differences in reaction to UVL shown by separate persons. These differences in reaction depend mainly upon the pigmentary content of the skin.

The absorption gradients of UVL in Type 1 and Type 2 skins are considered, and it is found that the only pronounced difference between the two is that a significant amount of energy is absorbed in the dermis of Type 1, while little passes the basal layer pigment of Type 2. It is our conclusion that the biological effects of UVL, which are more marked in persons of Type 1 than those in Type 2 are explained by this information. We therefore suggest that such biological effects are due to the absorption of UVL in the dermis.

We may then list the biological effects of UVL which are more marked in persons of Type 1 as follows:

(*a*) Physiological range
  (1) Erythema
  (2) Cornification
(*b*) Pathological range
  (1) Collagen degeneration
  (2) Skin cancer

These four responses to UVL should, on the principles listed above, be due to absorption of UVL in the dermis. Note that pigmentation definitely does not come into the list, as it is more marked in persons of Type 2 than in those of Type 1.

We point out that the condition called "senile elastosis" in North America and in Europe occurs even in teen-aged persons if they are fair-skinned and exposed to excessive amounts of solar radiation. It occurs only in exposed portions of the body, and, as well as having a characteristic histological picture, it also has a recognizable clinical appearance. Elastosis is but a stage in the process of connective tissue degeneration, and the ultimate appearance is often scarcely distinguishable from chronic radiodermatitis due to ionizing radiation. We call this condition "collagen degeneration" of the skin, and we have proven the following characteristics.

1. *Collagen Degeneration is Due to Ultraviolet Light.*—In advanced stages of collagen degeneration the overlying epidermis is atrophic. Fibroblasts resemble those seen in chronic radiodermatitis, and the production of fibrils in the dermis ceases. Vessels of the subpapillary plexus and later the vertical papillary loops become ectatic, and the sequence of events, in the evolution of the disorder, suggests that vascular injury ushers in the process.

2. *Collagen Degeneration Causes Profound Effects upon Nutrition of the Skin.*—Throughout the paper we emphasized the association of collagen degeneration of the dermis with skin cancer and certain other hyperplasias of the epidermis; we postulate a role for collagen degeneration in the genesis of skin cancer.

3. *Collagen Degeneration Plays an Important Role in Carcinogenesis.*—(*a*) Solar Keratosis: Collagen degeneration is a *sine qua non* in the diagnosis of solar keratosis. The epidermal lesion seems to follow the superimposition of a mild chronic dermatitis upon preexisting dermal changes. Epithelial hyperplasia is stimulated by the inflammatory reaction, but, owing to metabolic disturbances arising from the presence of collagen degeneration, a dyskeratosis is produced.

In discussing the genesis of solar keratosis we produce ample evidence that the pathogenic action of UVL must take place in the medium of the dermis. These arguments hold equally well for the role of UVL in all forms of skin cancer of solar causation.

(*b*) Keratoacanthoma: The same factors enter into the picture as in solar keratosis, but here the inflammation is more acute and may follow trauma or infection. The combination of inflammation and collagen degeneration is sufficient to produce the characteristic pseudoepitheliomatous lesion. When the inflammation subsides, the stim-

ulus to hyperplasia fails and the lesion regresses.

(*c*) Squamous-Cell Carcinoma: The factors at play in the causation of squamous-cell carcinoma are similar to those in solar keratosis. Squamous-cell carcinoma of solar origin is always preceded by collagen degeneration and almost always arises in a preexisting solar keratosis. The few cases of squamous-cell carcinoma of the skin of nonsolar origin occurring in Australia are not associated with collagen degeneration.

(*d*) Basal-Cell Carcinoma: In the etiology of basal-cell carcinoma the parts played by UVL and collagen degeneration are rather more complex. (1) Most cases of basal-cell carcinoma are due simply to the action of UVL, and they are preceded by collagen degeneration. (2) In others there is a nevoid tendency accelerated by the presence of collagen degeneration. (3) A further group has no collagen degeneration but, on clinical grounds, seems to have been produced by solar exposure. We presume that these lesions are due to the intensification of an inherent diathesis by a degree of solar exposure insufficient to produce visible degenerative change. (4) The few remaining cases have no solar component in their etiology, apparently being of purely endogenous origin. They, too, show no collagen degeneration.

9. Conclusion

Collagen degeneration of the skin arises in persons with inadequate cutaneous pigment from excessive exposure to solar radiation. By altering the nutrition of the epidermis, collagen degeneration predisposes to the development of solar keratoses, keratoacanthoma, squamous-cell carcinoma, and basal-cell carcinoma; when present in only moderate degrees it can intensify and accelerate other carcinogenic influences. Our final conclusion is that the carcinogenic effect of ultraviolet light is mediated by its primary action on the dermis.

The Department of Illustration, University of Sydney, supplied many of the photographs; Dr. H. O. Lancaster helped with the statistics; Dr. J. C. Belisario supplied a photograph of keratoacanthoma; Dr. K. Shaw-Smith and Dr. Ian Dawson assisted with the physiology.

Macquarie Chambers, 183 Macquarie St.

BIBLIOGRAPHY

Bachem, A., and Reed, C. I.: The Transparency of Live and Dead Animal Tissue to Ultra-Violet Light, Am. J. Physiol. 90:600, 1929.

——— and Reed, C. I.: The Penetration of Light Through Human Skin, Am. J. Physiol. 97: 86, 1931.

——— and Reed, C. I.: Skin and Radiation, Arch. Phys. Therapy 12:581, 1931.

Belisario, J. C.: The Malignant Tumours of the Skin, Australian J. Dermat. 4:179, 1954.

Blum, H. F.: Sunlight and Cancer of the Skin, J. Nat. Cancer Inst. 1:397-421, 1940.

Physiological and Pathological Effects of Ultraviolet Radiation, Ann. Rev. Physiol. 5:1, 1943.

Sunlight as a Causal Factor in Cancer of the Skin of Man, J. Nat. Cancer Inst. 9:247, 1948.

On the Mechanism of Cancer Induction by Ultraviolet Radiation, J. Nat. Cancer Inst. 11:463, 1950.

Edwards, E. A., and Duntley, S. Q.: Pigments and Color of Living Human Skin, Am. J. Anat. 65:1, 1939.

Eller, J. J., and Eller, W. D.: Tumors of the Skin: Benign and Malignant, London, Henry Kimpton, 1951.

Elliott, J. A., and Welton, D. G.: Epithelioma, Arch Dermat. & Syph. 53:307, 1946.

Engman, M. F.: External Cancer, J. A. M. A. 84: 103, 1925.

Finley, A. G.: Kerato-Acanthoma, Australian J. Dermat. 2:144, 1954.

Fouracres, F. A., and Whittick, J. W.: Relationship of Molluscum Sebaceum (Keratoacanthoma) to Spontaneously Healing Epithelioma of Skin, Brit. J. Cancer 7:58, 1953.

Hall, A. F.: Relationships of Sunlight, Complexion and Heredity to Skin Carcinogenesis, Arch. Dermat. & Syph. 61:589, 1950.

Hardy, J. D., and Muschenheim, C.: The Radiation of Heat from the Human Body: Emission, Reflection, and Transmission of Infra-Red Radiation by Human Skin, J. Clin. Invest. 13:817, 1934.

Keech, M. K.; Reed, R., and Wood, M. J.: Further Observations on the Transformation of Collagen Fibrils into Elastin: An Electron-Microscopic Study, J. Path. & Bact. 71:477, 1956.

Kirby-Smith, J. S.; Blum, H. F., and Grady, H. G.: Penetration of Ultraviolet Radiation into Skin, as a Factor in Carcinogenesis, J. Nat. Cancer Inst. 2:403, 1942.

Kovács, R.: Electrotherapy and Light Therapy, Ed. 5, London, Henry Kimpton, 1945.
Light Therapy, Springfield, Ill., Charles C Thomas, Publisher, 1950.

Lancaster, H. O.: Some Geographical Aspects of the Mortality from Melanoma in Europeans, M. J. Australia 1:1082, 1956.
——— and Nelson, J.: Sunlight as a Cause of Melanoma: A Clinical Survey, M. J. Australia 1:452, 1957.

Lansing, A. I.: Ageing of Elastic Tissue and the Systemic Effects of Elastase, in Ciba Foundation Colloquia on Ageing, London, J. & A. Churchill, Ltd., 1955.

Laurens, H.: The Physiologic Effects of Radiant Energy, Arch. Phys. Therapy 23:153, 1942.

Lucas, N. S.: The Permeability of Human Epidermis to Ultraviolet Irradiation, Biochem. J. 25:57, 1931.

Luckiesh, M., and Taylor, A. H.: Production of Erythema and Tan by Ultraviolet Energy, J. A. M. A. 112:2510, 1939.

Molesworth, E. H.: An Introduction to Dermatology, Sydney, Australia, Angus & Robertson, 1944, pp. 441-485.

Paul, C. N.: The Influence of Sunlight in the Production of Cancer of the Skin, London, H. K. Lewis & Co., 1918.

Percival, G. H., and Duthie, D. A.: Notes on a Case of Colloid Pseudomilium, Brit. J. Dermat. 60:399, 1948.

Rusch, H. P.; Kline, B. E., and Baumann, C. A.: Carcinogenesis by Ultraviolet Rays with Reference to Wavelength and Energy, Arch. Path. 31:135, 1941.

Ward, W. H.: The Problem of Skin Cancer, Australian J. Dermat. 1:157, 1952.
Nevoid Basal Cell Carcinoma with Porokeratosis of Mantoux, Australian J. Dermat. 4:47, 1957.

IF YOU CHANGE ADDRESS

Please notify us at least six weeks before you make the change.

With your notification, include the address label clipped from the latest copy of the journal. If your city has postal zone numbers, be sure to include the zone number in your new address.

You will want to get your copies promptly; so notify us at least six weeks in advance. Send your change notice to

A. M. A. Archives of Dermatology
American Medical Association
535 North Dearborn St.
Chicago 10, Illinois

The Use of Amodiaquin (Camoquin) in the Treatment of Polymorphous Light Eruption

MILTON M. CAHN, M.D.; EDWIN J. LEVY, M.D., and BERTRAM SHAFFER, M.D., Philadelphia

The antimalarial drugs quinacrine (Atabrine), chloroquine (Aralen), and hydroxychloroquine (Plaquenil) are effective agents for the prevention and treatment of polymorphous light eruption[1-6] and also for the treatment of discoid lupus erythematosus.[6,7]

A new antimalarial compound, amodiaquin (Camoquin), recently has been reported to be equally valuable in the treatment of discoid lupus erythematosus.[8,9]

The present study was done to evaluate the effectiveness of this drug in the treatment and suppression of polymorphous light eruption.

Nine patients with a history of recurrent prurigo and plaque-like forms of polymorphous light eruption were studied. These patients had had recurrences of their sunlight-induced eruption each summer, for periods ranging from 6 to 23 years. The eruption had been suppressed in eight of the nine patients during the preceding three summers (1953-1955) by chloroquine. The patients were not given suppressive antimalarial therapy during the spring and early summer of 1956 and were instructed to expose themselves to sunlight until their eruptions appeared. They were then given amodiaquin, 400 mg. per day for one week and 200 mg. per day thereafter, throughout the summer and fall, until Oct. 15, 1956. In April, 1957, prior to any eruption, these same patients were given amodiaquin in the same dosage schedule and were permitted unlimited sunlight exposure during the spring and summer.

Submitted for publication Feb. 26, 1958.

From the Department of Dermatology (Dr. Donald M. Pillsbury, Director). University of Pennsylvania School of Medicine.

Results

Amodiaquin was successful in the treatment of polymorphous light eruption in the nine patients studied during 1956. It was equally effective in preventing outbreaks in 1957, when given prior to exposure to summer sunlight (Table). No side-reactions were noted in this group.

Summary and Conclusions

Amodiaquin was effective in the treatment and suppression of polymorphous light eruption in nine patients. It successfully suppressed and also prevented an eruption in one patient in whom quinacrine, chloroquine, and hydroxychloroquine were ineffective.

1930 Chestnut St. (3).

REFERENCES

1. Cahn, M. M.; Levy, E. J., and Shaffer, B.: The Use of Chloroquine Diphosphate (Aralen) and Quinacrine (Atabrine) Hydrochloride in the Prevention of Polymorphous Light Eruptions, J. Invest. Dermat. 22:93-96 (Feb.) 1954.

2. Cahn, M. M.; Levy, E. J., and Shaffer, B.: Polymorphous Light Eruption: The Effect of

Results of Treatment with Amodiaquin in Nine Patients

Patient	Age	Sex	Duration of Polymorphous Light Eruption, Yr.	Results of Previous Antimalarial Therapy	Results with Amodiaquin
1	37	F	8	Chloroquine effective	Excellent
2	26	M	6	Chloroquine effective	Excellent
3	34	M	6	Ineffective (quinacrine, chloroquine, hydroxychloroquine)	Excellent
4	63	M	11	Chloroquine effective	Excellent
5	49	M	12	Chloroquine effective	Excellent
6	46	F	23	Chloroquine effective	Excellent
7	37	F	10	Chloroquine effective	Excellent
8	30	F	7	Chloroquine effective	Excellent
9	48	F	12	Chloroquine effective	Excellent

Chloroquine Phosphate in Modifying Reactions to Ultra-Violet Light, J. Invest. Dermat. 26:201-207 (March) 1956.

3. Levy, E. J.; Cahn, M. M., and Shaffer, B.: Polymorphous Light Eruption: Some Unusual Reactions in Ultraviolet Light Test Sites, J. Invest. Dermat. 28:147-153 (Feb.) 1957.

4. Woodburne, A. R.; Philpott, O. S., and Philpott, J. A., Jr.: Quinacrine (Atabrine) in Treatment of Solar Dermatoses, A. M. A. Arch. Dermat. & Syph. 70:116-118 (July) 1954.

5. Bennett, J. H., and Rees, R. B.: Plaquenil Sulfate in Treatment of Lupus Erythematosus and Light-Sensitivity Eruptions, A. M. A. Arch. Dermat. 75:181-183 (Feb.) 1957.

6. Knox, J. M.; Lamb, J. H.; Shelmire, B., and Morgan, R. J.: Light Sensitive Eruptions Treated with Atabrine and Chloroquine, J. Invest. Dermat. 22:11-16 (Jan.) 1954.

7. Pillsbury, D. M., and Jacobson, C.: Treatment of Chronic Discoid Lupus Erythematosus with Chloroquine (Aralen), J. A. M. A. 154:1330-1333 (April 17) 1954.

8. Pappenfort, R. B., and Lockwood, J. H.: Amodiaquin (Camoquin) in the Treatment of Chronic Discoid Lupus Erythematosus; Preliminary Report, with Special Reference to the Successful Response of Patients Resistant to Other Antimalarial Drugs, A. M. A. Arch. Dermat. 74:384-386 (Oct.) 1956.

9. Robinson, R. C.; Robinson, H. M., Jr., and Strahan, J. F.: Amodiaquin (Camoquin) in the Treatment of Discoid Lupus Erythematosus, Bull. School Med. Univ. Maryland 42:14-16 (Jan.) 1957.

A Simple Portable Skin Microscope for Surface Microscopy

LEON GOLDMAN, M.D., Cincinnati

The search for a simple inexpensive portable microscope for surface examination of the skin continues.[1] In a number of large centers of dermatology, the large stereobinocular skin microscopes on fixed stands are used for special case studies in examination of patients and for research. However, for the busy clinic, or for office practice, unfortunately it is still necessary to use a simple portable microscope.

Recently I have tried a microscope used by television technicians to examine single phosphor dots in the adjustment of the color-television tube. This is a cheap 8 in. microscope with magnification of × 25. The base is a clear plastic material which allows for the transmission of diffuse light at oblique angles to the surface of the skin. This plastic base can be cleansed very easily. The knurled knob on the side of the microscope allows for accurate focusing with the microscope body extended completely. The microscope has been found suitable for examination of various surfaces of the face, eyelids, lips, tongue, and scalp. With an intense light source it is possible to use this for examination of the skin and hair with light through a Wood filter. The obvious disadvantage of this portable instrument is, first, the absence of its own light source. This makes good illumination from outside necessary. The fluorescent light of the examining table, adequate daylight and examination spotlight do each furnish adequate lighting. Newer models have easier focusing for the elevated skin lesion. The necessity for keeping the microscope body continually extended is sometimes a little disadvantage when one carries the microscope around in his pocket. The magnifica-

Submitted for publication Feb. 26, 1958.

Skin microscope obtained from Bushnell Optical Corporation of America, Pasadena, Calif.

From The Department of Dermatology, University of Cincinnati College of Medicine.

Examination of the face with the modified portable television microscope.

tion, × 25, does not allow adequately for capillaroscopy. However, the blood vessels in the psoriasis lesion can be seen after adequate clearing of the skin. The magnification, × 25, is not excessive for pigmented skin lesions and tumors. Unfortunately, manufacturers, at least in the United States, are not interested in developing a plastic, lightweight, stereobinocular portable microscope, which would be the ideal portable skin microscope.

For an inexpensive portable skin microscope, or a skin microscope for the examining table in the office, the modified television microscope is the instrument of choice at present.

University of Cincinnati (21).

REFERENCE

1. Goldman, L.: Clinical Studies in Microscopy of the Skin at Moderate Magnification, A. M. A. Arch. Dermat. 75:345, 1957.

Eidamella Spinosa — Pathogenic for Man?

M. PAUL LAZAR, M.D., and HELEN MacLEAN, M.S., Chicago

Discovering the unusual is always exciting, particularly when it is associated with the routine of office practice.

This occurred when a 62-year-old white male printer consulted one of us (M. P. L.) in 1955. He had a chronic dermatitis of the hands and had been subject to repeated episodes of hand eruptions for 25 years. No laboratory investigations were done during this period.

A more persistent dermatitis began in 1952, and clinical cure followed the use of x-ray therapy and topical remedies. However, a recurrence (or a new eruption?) appeared within six months, and therapy could not prevent its progression. By 1955, both palms were markedly hyperkeratotic, dry, and scaling. No inflammation was evident, and several fingernails were dystrophic. In addition, an erythematous, dry, scaling, eczematous dermatitis associated with a papular and folliculopustular eruption was present in the groins. Mild plantar hyperkeratosis, interdigital scaling, and minimal nail dystrophy were evident on the feet. The entire skin surface was generally dry, with keratosis pilaris obvious on the back, arms, and legs. A universal decrease in body hair was noticeable, with that present being confined primarily to the scalp, beard, axillae, and genital areas; normal male hair distribution was manifest. He was in good health generally except for diabetes mellitus controlled by diet and 8 units of protamine zinc insulin daily.

Material for fungus studies was taken from the fingernails, palms, groins, and toenails at the first visit and several times afterwards. Microscopic evidence of fungi was present, and positive cultures on Sabouraud's medium were always accompanied by a bright red pigment diffused throughout the medium. The organism was thought by one of us (M. P. L.) to be Trichophyton gallinae, and, because of its rarity in human infections, confirmations were sought. One of us (H. M.), at the Michael Reese Hospital Microbiology Laboratory, could not identify the growth as any of the usual pigment-producing dermatophytes. Final identification of the culture as a strain of Eidamella spinosa was made by Dr. Margarita Silva, of the Department of Dermatology, in the Columbia University College of Physicians and Surgeons. Dr. Edward De Lamater, of the University of Pennsylvania, concurred in the identification. The unusual discovery did not aid us clinically, as the dermatitis of the hands was progressive and therapy did not prevent involvement of all the fingernails.

The only plausible sources of infections were three parakeets, two of which died. The third was given to a friend living in another city. According to the patient, all three birds had bald scaling areas and appeared ill. Unfortunately, the one live parakeet was not seen, and attempts to culture fungi from feathers mailed us were unsuccessful.

Comment

To the best of our knowledge, no case of human infection with E. spinosa has been reported in the world literature. The organism was first reported by Matruchot and Dassonville[1,2] in 1901, after the fungus was recovered from a dog. Conant[3] cultured it in 1935 from a human fingernail but did not believe the organism pathogenic. An excellent and comprehensive discussion of E. spinosa was published by De Lamater,[4] in 1937.

Pathogenicity of the organism for our patient is supported by the following features: 1. The fungus was recovered from four different sites of clinical disease. 2. No other organism which could cause

Received for publication Feb. 26, 1958.

From the Departments of Dermatology and Microbiology, Northwestern University Medical School and Michael Reese Hospital.

such a clinical picture was isolated. 3. The clinical disease was progressive while the patient was under observation and therapy. 4. The organism could not be recovered again from the sites of infection which cleared.

Lack of support for the pathogenicity of this organism rests with the following factors: 1. Attempted inoculation of a human was done once without causing disease. 2. It has never been isolated and identified as a cause of human disease. 3. Most of our cultures were contaminated; perhaps an organism not identified caused the disease.

Speculations about finding this unusual fungus are inevitable. Did the repeated bouts of dermatitis, constant exposure to irritants, xeroderma as evidenced by the keratosis pilaris, and previous x-ray therapy predispose the patient to infection with this organism? Is the organism likelier to grow on the diabetic skin? Perhaps these situations are necessary to make man fertile for this gymnoascaceous fungus. As was stated by De Lamater in 1937, "The question whether *Eidamella spinosa* is truly a pathogen or only a facultative parasite is, then, still an open one." However, it is our feeling that this strain of the fungus was the cause of the clinical picture seen, though it may have been aided by the predisposing situations mentioned. Where did the patient contact the organism, one reported just three times and in geographical areas so far removed from each other?

Perhaps a more diligent search for the organism and its natural habitat (nonhuman hosts, vegetation, or soil) will supply a more complete understanding of E. spinosa. Apparently, it is widespread, having been found in France, Massachusetts, and Illinois.

The clinical features of the disease in one patient and the generally poor response to therapy are similar to those in Trichophyton rubrum infections.

Summary

Eidamella spinosa was found in a routine office culture. Its relationship to a dermatological condition is discussed.

30 N. Michigan Ave.

REFERENCES

1. Matruchot, L., and Dassonville, C.: Eidamella spinosa, dermatophyte produsiant des peritheces, Bull. Soc. mycol. France 17: 123, 1901.

2. Matruchot, L., and Dassonville, C.: Sur les Teignes du chien, Bull. Soc. centr. méd. vét. 56:50, 1902.

3. Conant, N. F.: Personal communication to the authors.

4. De Lamater, E. D.: Eidamella Spinosa (Matruchot and Dassonville) Refound, Mycologia 29:572, 1937.

Granuloma Faciale

Report of a Case

GEORGE F. PRICE, M.D., Brooklyn

In the February, 1947, issue of the *Archives of Dermatology and Syphilology* a résumé, consisting of four articles, on the subject of eosinophilic granuloma of the skin, appeared.

Dobes and Weidman discussed the case of granulomatous Hodgkin's disease of the skin with extreme eosinophilia. They thought that their thinking was too extreme to classify this as a case of eosinophilic granuloma but left the door open for it to qualify in the future, if such an entity as eosinophilic granuloma should be established.[1]

Lewis and Cormia discussed the theoretic and practical considerations based on the study of a case of eosinophilic granuloma.[2] Lever discussed the eosinophilic granuloma of the skin in relation to erythema elevatum diutinum and eosinophilic granuloma of the bone.[3] Weidman discussed the eosinophilic granulomas of the skin.[4]

In the October, 1948, *Archives of Dermatology and Syphilology*, Lever, Lane, Downing, and Spangler reported three cases. Microscopic examination in all revealed eosinophils and histiocytes.[5]

In the November, 1949, issue of the *Archives of Dermatology and Syphilology*, Oliver, Webster, Ginsberg, and Steinberg reported two more cases.[6]

In the March, 1950, issue of the *Archives of Dermatology and Syphilology*, Cobane, Straith, and Pinkus discussed the relation to other eosinophilic granulomas of the skin and to reticulogranuloma.[7]

In the July, 1950, issue of the *Archives of Dermatology and Syphilology*, Lever and Leeper discussed three cases representing two different diseases described as eosinophilic granuloma—one

Submitted for publication Feb. 10, 1958.

a bone lesion in conjunction with cutaneous lesions and the other disease having only cutaneous lesions.[8]

In the February, 1952, issue of the *A.M.A. Archives of Dermatology and Syphilology,* Peck Palitz, and Reiner reported two cases substantiating the concept of a new entity, facial granuloma with eosinophilia, as described by Cobane, Straith, and Pinkus and by Lever and Leeper. They gave an excellent differential diagnosis, considering erythema perstane, granuloma annulare, discoid lupus, lymphocytoma, leukemia cutis, erythema elevatum diutinum, sarcoid lesions, leprosy, mycosis fungoides, syphilis, and drug eruption.[9]

In the March, 1953, issue of *Postgraduate Medicine,* Cawley and Wheeler tried to correlate and consolidate all the vast complex conglomeration of data covering the subject of eosinophilic granuloma.[10]

In the March, 1951, *Medical Clinics of North America,* Pinkus discussed in great detail granuloma with eosinophilia, and, as a result of his intensive survey, he concluded that the term "eosinophilic granuloma" had outlived its usefulness and should be forgotten.[11]

In "The 1952 Year Book of Dermatology and Syphilology," Pinkus discussed seven cases and suggested the name "Granuloma faciale."

The world literature, the history, and the bibliography are adequately covered in the above articles, and the reader is referred to them for case reports and more detailed discussion of all facets of the subject.

Report of Case

A 41-year-old married man, born in the United States, a clerk by occupation, was seen on Dec. 15, 1947, with multiple lesions, some discrete but some confluent, on the face which were darkly pigmented about the periphery, had a shiny atrophic center, and were roughly in a butterfly distribution (Fig. 1). The lesions were of five years' duration. He received 20 intramuscular injections of bismuth subsalicylate, 2 cc. each, the last one on June 3, 1948. I did not see him again until Oct. 15, 1948, when he received four more intramuscular injections of bismuth subsalicylate, 2 cc. each. I did not see him again until Jan. 23, 1957, when he came into my office with, as he said, the same lesions, there being no change whatsoever. I gave the patient 250 mg. of chloroquine (Aralen) q. i. d., with no resulting improvement. On Feb. 8, 1957, a biopsy specimen was taken from a lesion on the forehead, and, although there was no definite diagnosis, Dr. William Moitrier, Brooklyn, definitely ruled out sarcoidosis and discoid lupus erythematosus. On Feb. 12, 1957, the patient was presented before the members of the Brooklyn Dermatological Society, and discoid lupus, sarcoidosis, and the most agreed-upon diagnosis, eosinophilic granuloma, were considered. As shown in Figure 1 there was slight atrophy with no scarring such as you would expect to see in lupus erythematosus of such long standing. The lesions were mostly isolated, discrete, and of irregular shape and outline, although there was some confluence of the lesions on the temples. The lesion of the nose was hypertrophic and erythematous. The other lesions were brown and tawny; some showed a pale atrophic-like center, as though healing had occurred, although the patient stated that no change had ever taken place. Yearly x-rays of his chest and Wassermann tests done by his employer every year since 1945, were always negative. However, on the last check-up, on Dec. 23, 1955, he showed hypertension, with blood pressure of 204/140, and there was a trace of albumin in the urine. After the patient was presented at

Fig. 1.—Characteristic butterfly distribution of the rash, consisting of isolated discrete and confluent lesions.

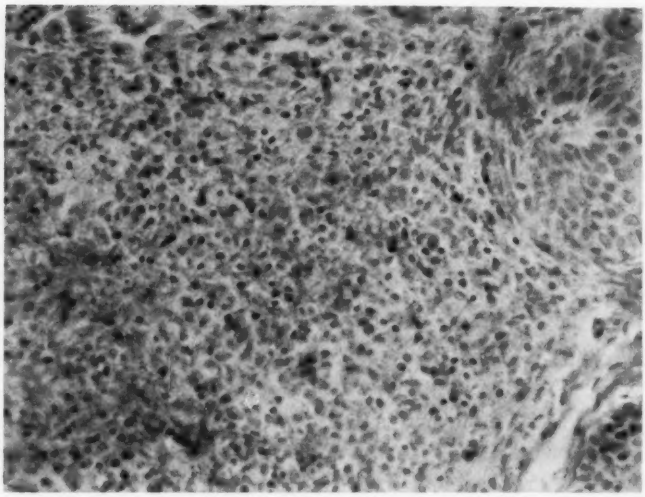


Fig. 2.—High-power view shows the multicellular characteristic of the infiltrate, which includes eosinophils, histiocytes, plasma cells, and polymorphonuclear cells.

the Brooklyn Dermatological Society, it was suggested that he be given arsenic therapy, internally, and 10 drops of potassium arsenite (Fowler's) solution three times a day was ordered. At the end of three weeks of such therapy, there was no improvement. On March 10, 1957, he was seized with a coronary occlusion, and died on March 11, 1957. No autopsy was obtained.

The case created such discussion and curiosity that a colleague stated that if I consulted "The 1952 Year Book of Dermatology and Syphilology" I would find a description of my own case. As a result, Dr. Hermann Pinkus, Monroe, Mich., agreed to review the slides and Kodachrome transparencies, and he stated, "the histopathologic picture appears characteristic. There is the mixed granulomatous infiltrate, more or less centered around wide blood vessels. There are numerous leukocytes around these vessels and quite a few eosinophils seem to be present. The rest of the corium is occupied by histiocytes, with some pigment, probably hemosiderin (although melanin also occurs) and, of course, lymphocytes and some plasma cells also are present. The infiltrate usually keeps a certain distance from the epithelial structures, at least has no tendency to invade them" (Figs. 2 and 3).

Comment

The lesions are on the face, may be single or multiple, and are circumscribed, soft, plaque-like,

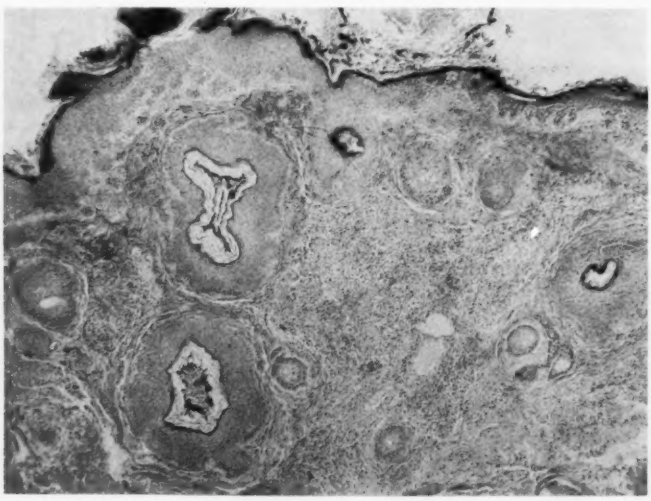


Fig. 3.—Low-power view showing the intense perivascular involvement, the free zone of the cutis in the upper layer, and the absence of infiltration and involvement of the epidermis.

of long duration, persistent, and nonsuppurative. The color varies from red to brown and tawny; they are asymptomatic, and the etiology is not known. They are resistant to all forms of therapy, except surgery, and, even then, recurrences have been reported. The general condition of the patient is not affected by the lesions per se.

I believe that this case conforms to all the criteria necessary to sustain a diagnosis of granuloma faciale, as suggested by Pinkus.

Dr. William Moitrier and Dr. Hermann Pinkus cooperated and assisted in this study, and Mr. Herbert Z. Fischler, of the Jewish Hospital for Chronic Diseases, did the photography.

66 Rutland Ave. (25).

REFERENCES

1. Dobes, W. L., and Weidman, F. D.: Granulomatous Hodgkin's Disease of the Skin with Extreme Eosinophilia, Arch. Dermat. & Syph. 55: 212-221 (Feb.), 1947.

2. Lewis, G. M., and Cormia, F. E.: Eosinophilic Granuloma, Arch. Dermat. & Syph. 55:176-191 (Feb.) 1947.

3. Lever, W. F.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. 55:194-211 (Feb.) 1947.

4. Weidman, F. D.: The Eosinophilic Granulomas of the Skin, Arch. Dermat. & Syph. 55:155-175 (Feb.) 1947.

5. Lever, W. F.; Lane, C. G.; Downing, J. G., and Spangler, A. S.: Eosinophilic Granuloma of the Skin: Report of 3 Cases, Arch. Dermat. & Syph. 58:430-438 (Oct.) 1948.

6. Oliver, E. A.; Webster, J. R.; Ginsberg, J. E., and Steinberg, H. S.: Eosinophilic Granulomas of the Skin, Arch. Dermat. & Syph. 60:701-716 (Nov.) 1949.

7. Cobane, J. H.; Straith, C. L., and Pinkus, H.: Facial Granulomas with Eosinophilia, Arch. Dermat. & Syph. 61:442-454 (March) 1950.

8. Lever, W. F., and Leeper, R. W.: Eosinophilic Granuloma of the Skin, Arch. Dermat. & Syph. 62:85-96 (July) 1950.

9. Peck, S.; Palitz, L. L., and Reiner, E.: Facial Granuloma with Eosinophilia (Granuloma Faciale), A. M. A. Arch. Dermat. & Syph. 65: 216-223 (Feb.) 1952.

10. Cawley, E. P. and Wheeler, C. E.: Granulomas with Tissue Eosinophilia (Eosinophilic Granuloma), Postgrad. Med. 13:228-230 (March) 1953.

11. Pinkus, H.: Granulomas with Eosinophilia ("Eosinophilia Granuloma"), M. Clin. North America 35:463-477 (March) 1951.

12. Pinkus, H.: Granuloma Faciale, in the 1952 Year Book of Dermatology and Syphilology, edited by M. B. Sulzberger and R. L. Baer, Chicago, The Year Book Publishers, Inc., 1952, pp. 255-257.

Oral-Perioral Leukokeratosis

FRANCESCO RONCHESE, M.D., and ARTHUR B. KERN, M.D., Providence, R. I.

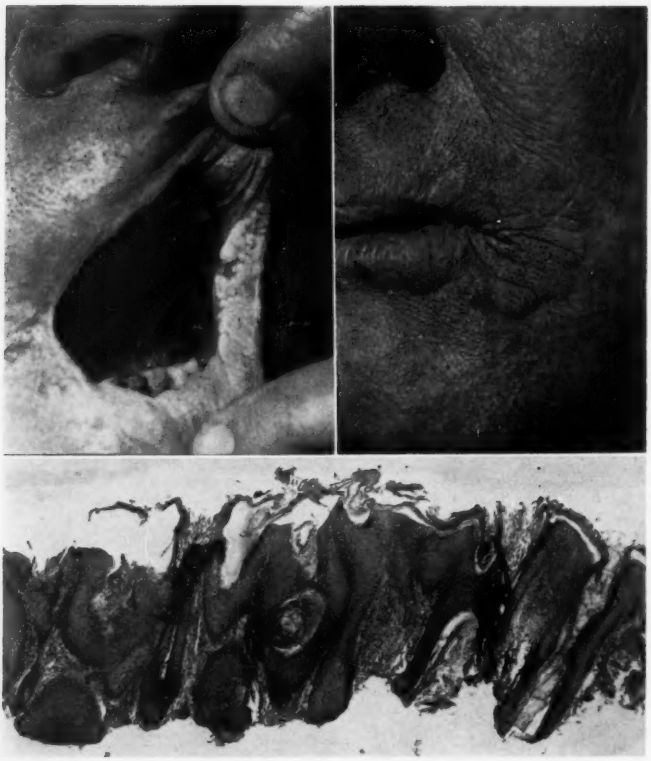
A 57-year-old man, first seen in June, 1952, complained of thick white areas, of eight years' duration, about the left oral commissure. There was no discomfort. The process gradually extended peripherally, and at the same time changes in the mucosa of the cheeks and lower lip were noted. He had contracted syphilis in 1917 and had received treatment in 1937 and in 1949. He was a cigar smoker and usually held the cigar on the left side of his mouth.

The white thickened plaques involved the buccal mucosa, hard palate, and lower lip; a similar process was noticeable on the skin about the left oral commissure. On several occasions white thick eroded plaques on the buccal mucosa and lip were removed electrosurgically. Treatment otherwise was limited to a course of chloroquine, which had no effect on the lesions. During recent years he has presented numerous vague complaints referable to his throat and gastrointestinal tract, and on one occasion he was admitted to a mental hospital.

Numerous biopsy sections have been obtained from the cutaneous and mucosal lesions. These have usually been reported as senile keratosis or leukoplakia, although one was reported as consistent with lupus erythematosus. Serologic tests for syphilis during the period of observation have been very weakly positive. Chest x-ray, fluoroscopy, and spinal fluid examinations in 1952 showed no abnormalities.

In October, 1956, the patient was presented at a meeting of the New England Dermatological Society. At that time the suggested diagnoses included lupus erythematosus, tertiary syphilis, and an unusual form of leukoplakia. It is our opinion, however, that the clinical and histopathologic features presented rule out these diagnoses. A witty

Submitted for publication March 3, 1958.



Oral-perioral peculiarly patterned leukokeratosis.

Gallic author referred to certain annular cutaneous lesions as "syphilides élégantes."[1] The ornate pattern of our patient's perioral lesions could be called "elegant hyperkeratoses."

This case is reported as a perhaps hitherto undescribed oral and perioral patterned hyperkeratotic disorder of unknown etiology.

REFERENCES

1. Lefranc, M.: Syphilides cutanées "élégantes" chez un noir Algérien, Ann. mal. vén. 34:32 (Jan.) 1939.

170 Waterman St. (6).

Dermatitis of the Face Caused by Guanine in Pearly Nail Lacquer

CONRAD STRITZLER, M.D., Jamaica, N. Y.

Dermatitis of the eyelids, face, and neck due to sensitivity to an ingredient in nail lacquer, chiefly the formaldehyde-sulfonamide resin used as a means of imparting luster to the lacquer film,[1,2] is well known. During the past year I have seen four patients with a patchy eczematous contact-type dermatitis of the eyelids, face, chin, and neck who gave negative results with patch tests with ordinary nail lacquer but positive results with patch tests with pearly or frosted nail lacquer.

Submitted for publication Feb. 24, 1958.

Associate Professor of Dermatology and Syphilology, State University of New York College of Medicine, Downstate Medical Center, Brooklyn.

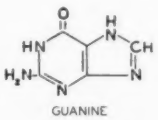


Figure 1

Patch tests with the various ingredients in the nail lacquer, including the solvent, plasticizer, resin, and pigment, were negative, but patch tests to the pearly material were positive. The pearly material is made from the fish scales of sardines and consists chiefly of guanine. Patch tests with pure powdered guanine and powdered defatted sardine fish scales were positive in all 4 patients and negative in 20 controls. Patch tests with pure powdered guanine were positive in all 4 patients and negative in 20 controls. All patients were able to use ordinary nail lacquer not containing the guanine without cutaneous reaction.

Patch tests with olive-oil extracts of skinless and boneless sardines and with the sardine meat were negative. All of the patients had eaten sardines, with and without the skin and scales, with no obvious reaction. None of them had handled the sardine scales or sardine skins previously.

I have been unable to find mention in the literature of dermatitis of the face caused by guanine in pearly nail lacquer. Guanine is a purine derivative obtained by hydrolysis of nucleic acid. The structure of guanine is illustrated in Figure 1.

Patch tests with adenine, uric acid, caffeine, theobromine, and adenylic acid were all negative, suggesting that the NH_2 in the 2 position was essential to provoke the reaction. The relation of these purine derivatives is clarified by the structural formulas in Figure 2.

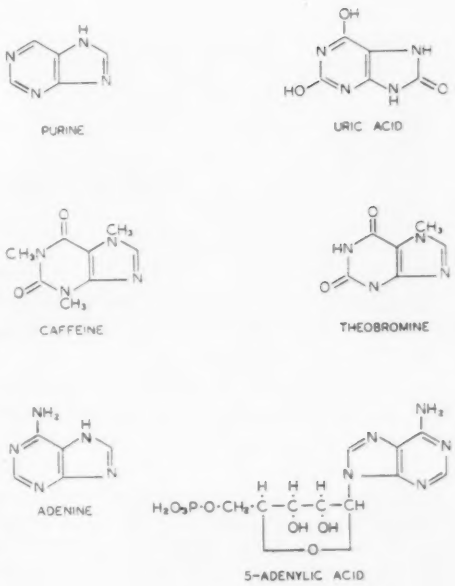


Figure 2

Summary

A group of four patients with a patchy contact dermatitis of the face and neck, proven to be caused by acquired allergic contact sensitivity to guanine in pearly nail lacquer, is reported. There was no cross sensitization with other purines.

90-26 148 St. (35).

The Revlon Cosmetic Company, New York, cooperated in this study.

Addenum

Since this article was written, one of these patients, who was previously able to tolerate clear nail lacquer without guanine, has developed a recurrence of the dermatitis of the face and neck following the use of this material. Patch tests were originally negative to clear lacquer but are now positive. Patch tests with the ingredients of the lacquer show a positive reaction to the sulfonamide resin used to impart luster to the lacquer film.

REFERENCES

1. Wise, F., and Sulzberger, M. B.: 1942 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1943, pp. 78-79.

2. Osborne, E. D.; Jordan, J. W., and Campbell, P. C., Jr.: Dermatitis Venanata Due to Lacquer, Arch. Dermat. & Syph. 44:604-615 (Oct.) 1941.

3. Conant, J. B.: Chemistry of Organic Compounds: A Year's Course in Organic Chemistry, New York, The Macmillan Company, 1942, p. 526.

Scientific Exhibits

The Human Ear Canal

ELDON T. PERRY, M.D., D.Sc. (Med.)

and

WALTER B. SHELLEY, M.D., Ph.D.

Philadelphia

The external ear canal is a highly distinctive anatomical site, both geometrically and histologically. It is a small restricted area, and yet commonly it presents dermatologic problems, at times limited solely to this area. This exhibit presents the significant information available concerning the human ear canal. The basic histologic characteristics of this skin, as well as the salient physiologic features, are presented. It can be seen that in the few millimeters of ear canal one passes from an appendageless and extremely thin skin to one which is richly supplied with both sebaceous and apocrine glands. In addition, histologic studies are presented both from our experimental studies and from clinical biopsy material which show the wide range of disturbances which may occur in the ear canal.

Histology

Cartilaginous Canal

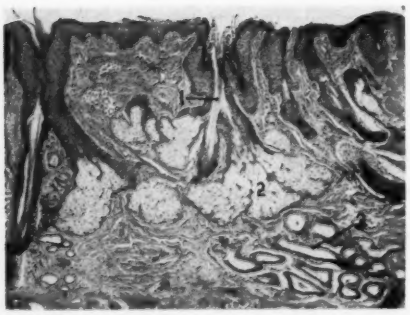


Fig. 1.—(*1*) Hair; (*2*) superficial pad of sebaceous glands; (*3*) deeper layer of ceruminous (apocrine) glands. Note absence of eccrine sweat glands.

Based on studies supported by United States Public Health Service Research Grant 4231.

From the Department of Dermatology (Dr. Donald M. Pillsbury, Director), University of Pennsylvania School of Medicine.

Shown as a scientific exhibit of The American Academy of Dermatology and Syphilology at the 14th Annual Meeting, Chicago, Dec. 3-8, 1955.

Shown as a scientific exhibit of the Section on Dermatology at the 105th Annual Meeting of the American Medical Association, Chicago, June 11-15, 1956.

Bony Canal

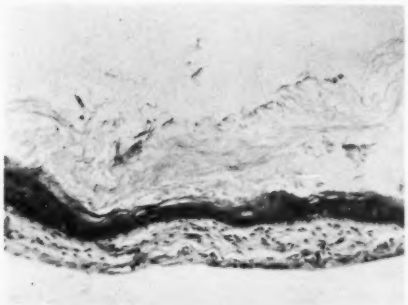


Fig. 2.—No skin appendages. No rete ridges. Epidermis and dermis are very thin.

Axilla

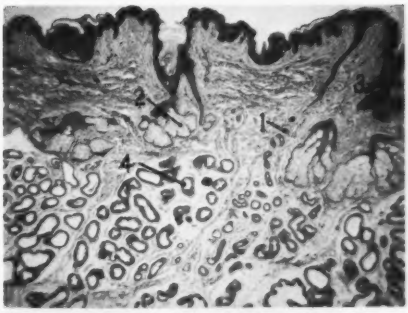


Fig. 3.—(*1*) Eccrine glands; (*2*) sebaceous glands; (*3*) hair; (*4*) large apocrine glands.

The Appendages of the Skin of the Cartilaginous Canal

1. *Ceruminous (Apocrine) Gland*

A. Duct

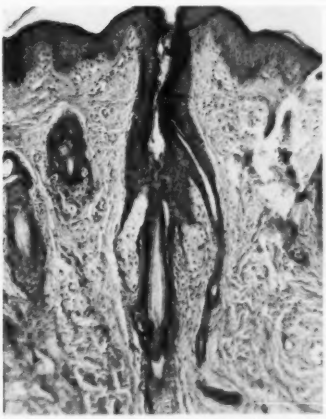


Fig. 4.—Follicular opening.

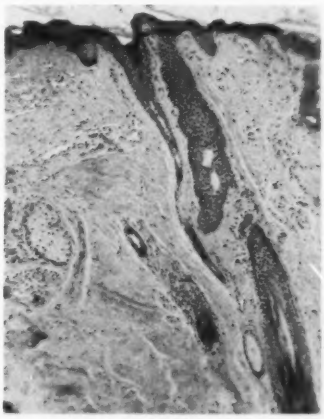


Fig. 5.—Extrafollicular opening.

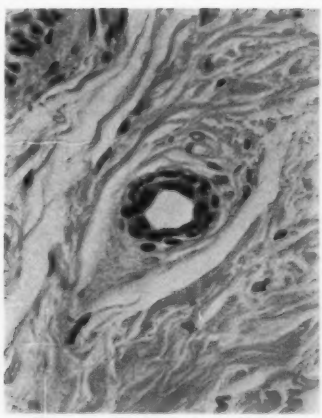


Fig. 6.—Deeper duct in cross section.

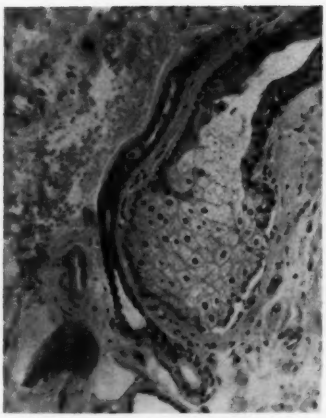


Fig. 7.—Longitudinal section.

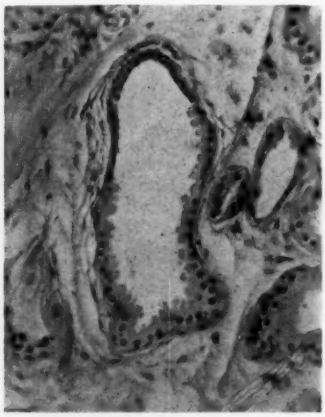


Fig. 8.—Transition from gland to duct.

B. Gland

Fig. 9.—Pigment granules.

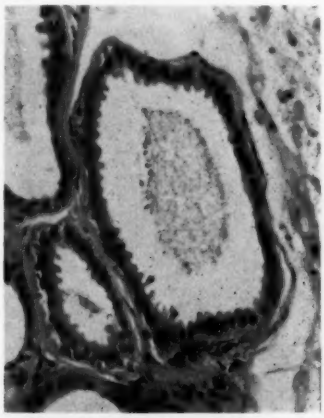


Fig. 10.—Secretory buds (artifact?).

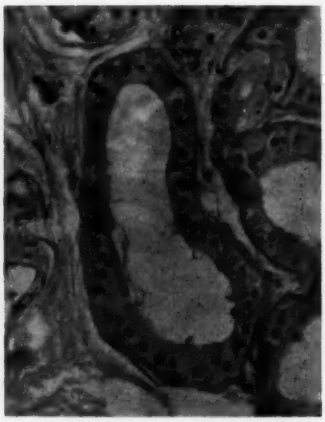


Fig. 11.—Layers of the gland wall.

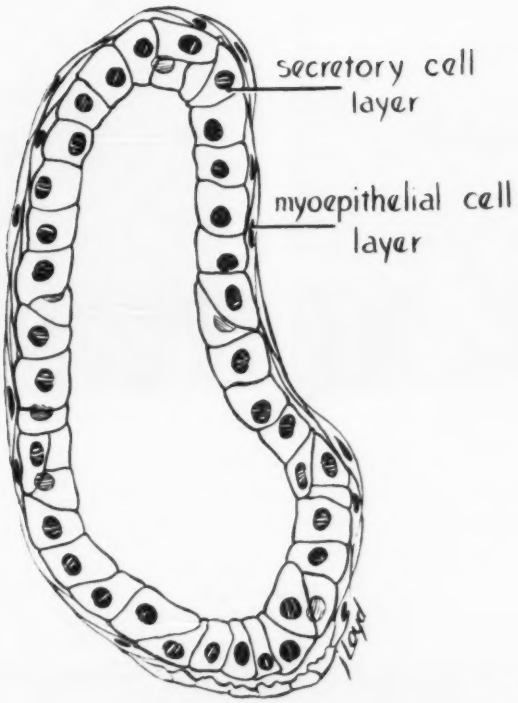


Fig. 12.—Sketch of Figure 11.

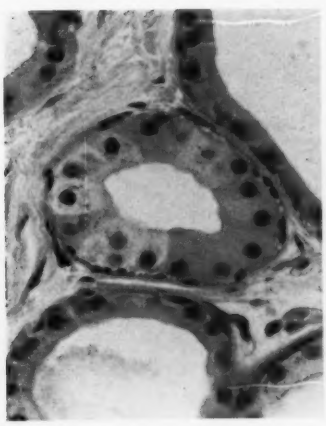


Fig. 13.—Lighter-staining cells.

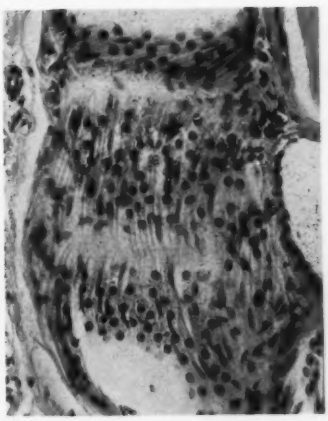


Fig. 14.—Myoepithelium.

2. *Sebaceous Gland*

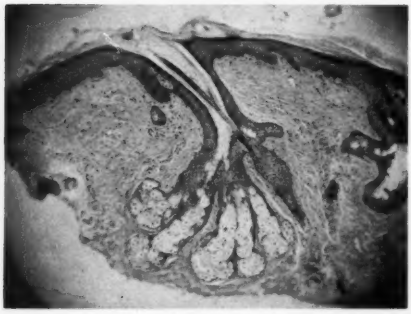


Fig. 15

3. *Hair Innervation*

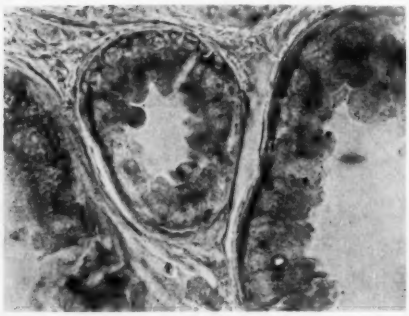


Fig. 16.—Nerve fibers around ceruminous gland.

Physiology

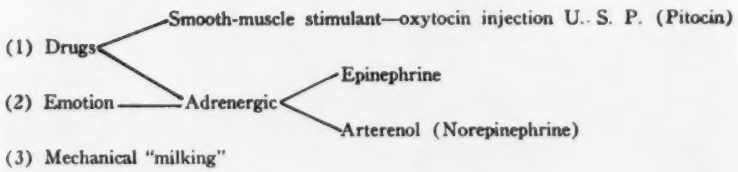
Sebum+Ceruminous-Gland (Apocrine Sweat) Secretion=Cerumen

The factors which control sebaceous gland secretion are not known, but the process is a steady, continuous one of a holocrine nature.

Ceruminous-gland activity may be divided into two phases: (1) secretion—formation of the secretory product; (2) "sweating"—delivery of preformed secretion to the skin surface.

The factors which control the formation of ceruminous-gland secretion are not known.

The ceruminous gland "sweats" in response to the following stimuli:



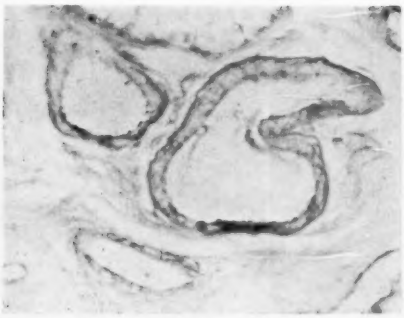


Fig. 17.—Ceruminous (apocrine) sweat gland. No glycogen.

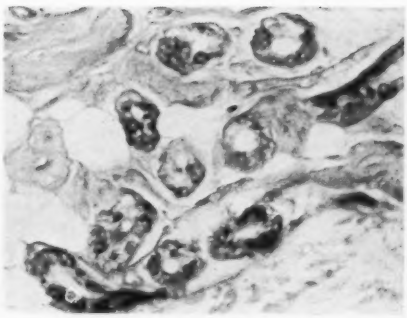


Fig. 18.—Eccrine sweat gland. Glycogen present.

Eccrine sweat is formed intermittently. The eccrine gland uses stored glycogen for energy. The ceruminous gland, like other apocrine glands, forms secretion continuously, utilizing some other, as yet unknown, source of energy; Hotchkiss-McManus stain.

Fig. 19.—Highly magnified view of apocrine sweating in ear canal.

Experimental Pathology

Fig. 20.—Plugging of the apocrine ducts following adhesive tape application.

Fig. 21.—Dilatation of apocrine ducts following adhesive tape application.

Fig. 22.—Rupture of apocrine ducts following adhesive tape application.

Fig. 23.—Inflammatory infiltrate following rupture of apocrine ducts.

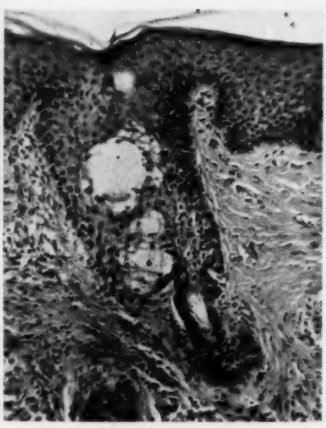


Fig. 25. Histologic picture of apocrine miliaria in the ceruminous gland.

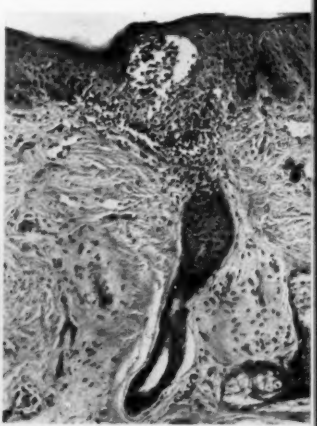


Fig. 24.—Vesicle formation in epidermis as a result of apocrine sweat retention.

Apocrine Miliaria of the External Auditory Canal

If adhesive tape is applied to the wall of the external ear canal and left in place for several weeks, plugs may form in the ducts of some apocrine glands (Fig. 20). The proximal portion of the duct may then dilate (Fig. 21), or rupture (Fig. 22), allowing apocrine sweat to escape into the surrounding epidermis. This may call forth an inflammatory infiltrate (Fig. 23) or cause the formation of an intraepidermal vesicle (Fig. 24). The full-blown picture of apocrine miliaria in the ceruminous gland (Fig. 25) resembles the histologic picture of Fox-Fordyce disease as seen in axilla.

Retention of Sebum

The duct of a normal sebaceous gland (Fig. 26) may, under experimental conditions, become plugged, resulting in the retention of sebum and in dilatation (Fig. 27). "Sebaceous miliaria" has not been seen.

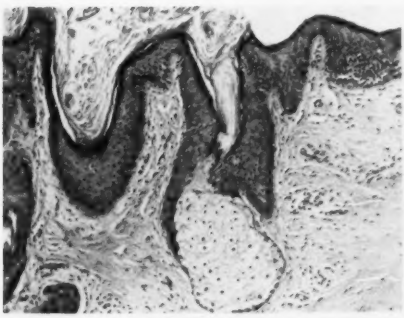


Figure 26

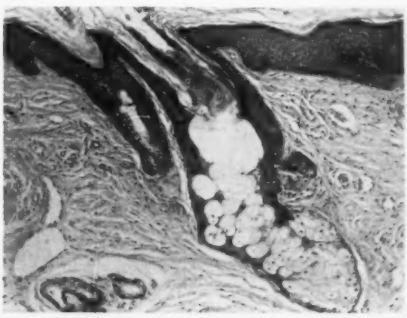


Figure 27

Clinical Pathology

Otitis externa may have any number of causes. These photomicrographs illustrate a few. (Histologic readings by Dr. Margaret Gray Wood.)

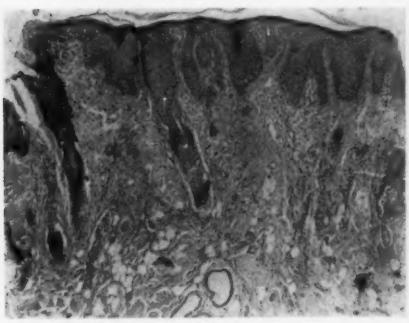


Fig. 28.—Psoriasis.

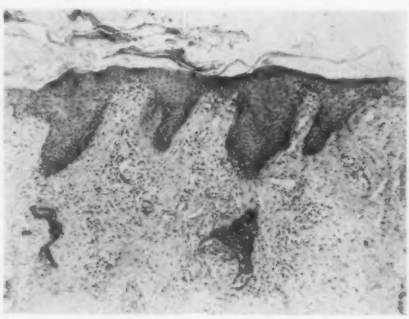


Fig. 29.—Seborrheic dermatitis.

Fig. 30.—Neurodermatitis.

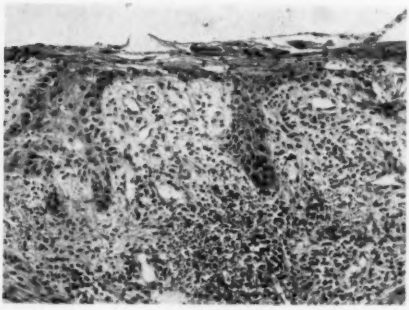


Fig. 31.—Chronic discoid lupus erythematosus.

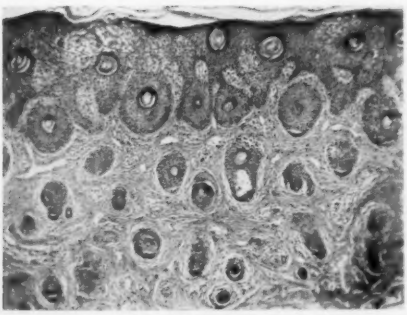


Fig. 32.—Infectious eczematoid dermatitis.

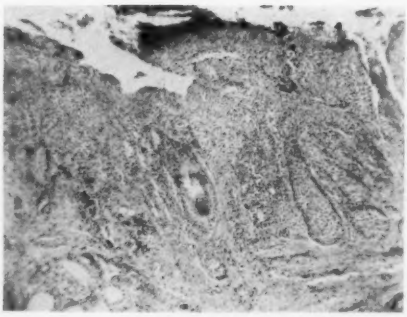


Fig. 33.—Exfoliative dermatitis.

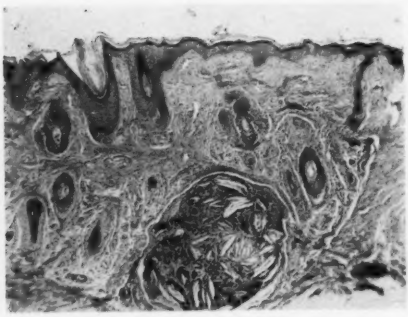


Fig. 34.—Foreign-body reaction.

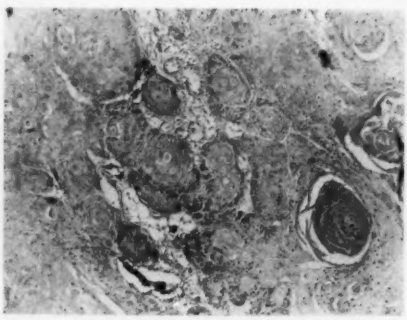


Figure 35.—Carcinoma.

Figure 36.—Letterer-Siwe disease.

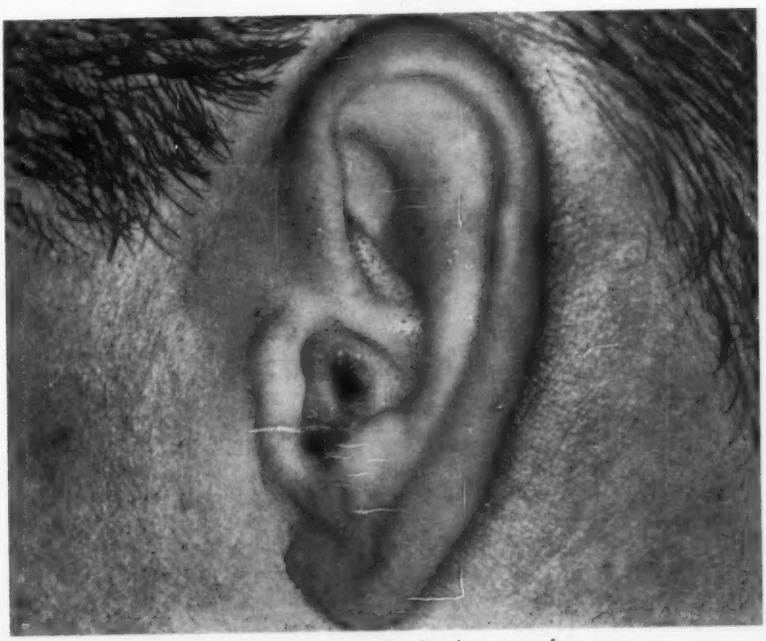


Fig. 37.—Apocrine sweat droplets in ear concha.

Obituaries

JAMES R. WEBSTER
1906-1958

On Friday, Feb. 28, 1958, the Chicago Dermatological Society lost a distinguished and beloved member, Dr. James R. Webster. Dr. Webster was born in Chicago on Oct. 16, 1906, the son of Dr. Ralph Waldo and Grace Webster. James Webster received his academic education at the University of Chicago where he received a Bachelor of Science degree in 1927. At the University of Chicago, he was All Conference baseball catcher for two consecutive years, and with the entire team, he traveled to Japan in 1925. He received his M.D. degree at Rush Medical College in 1932, interned at Presbyterian Hospital, and was assistant to Oliver Ormsby, 1932-1933 and 1935-1936. He did postgraduate work in dermatology with Professor Otto Kren in Vienna, 1932-1934. He also spent time in the dermatologic clinics of Zurich, Paris, and London. Upon his return

JAMES R. WEBSTER
1906-1958

to Chicago, his academic rise was rapid. He began as Clinical Associate in dermatology at Rush in 1935, and by 1950, he was Professor of Dermatology at Northwestern University Medical School. He was certified by the American Board of Dermatology in 1937 and was elected to the American Dermatological Association in 1950. During World War II, Webster joined the A. U. S. in 1942, with the rank of captain and was separated from the Service March, 1946, with the rank of Major. He was awarded the Bronze Star medal. He served as the

Eulogy read at the meeting of the Chicago Dermatological Society, March 19, 1958.

Skin Consultant in the SWPA Theatre. His hospital appointments were many. He was Attending Dermatologist at Cook County Hospital, Children's Memorial Hospital, Lutheran Deaconess Hospital, Hines Veterans' Hospital, and Chicago Wesley Memorial Hospital. He was the Veterans' Administration Area Consultant in Dermatology.

Dr. Webster was married to Ruth M. Burtis on Sept. 4, 1930, and was the father of two sons, James R. Webster, M.D., and Stephen R. Webster, a medical student at Northwestern University Medical School. James Webster was a fourth generation physician. His great grandfather was Dr. John Randolph Webster, who graduated from Jefferson Medical College in 1837, and in the same year settled in Monmouth, Ill., where he was a pioneer physician. His grandfather, Dr. John R. Webster, graduated from Rush Medical College in 1858 and practiced in Monmouth. He served as a surgeon in the Union Army during the Civil War. His father, Dr. Ralph Waldo Webster, graduated from Rush Medical College in 1898 and was distinguished Professor of Toxicology and Legal Medicine in his alma mater.

Dr. Webster was very active in the Chicago Dermatological Society and in the American Academy of Dermatology and Syphilology. In 1952, he became President of the Chicago Dermatological Society. Also, in 1952, he was elected Assistant Secretary-Treasurer of the American Academy of Dermatology and Syphilology and worked with Dr. Rauschkolb up to Dr. Rauschkolb's untimely death in April, 1955. He was then elected Secretary-Treasurer at the 1955 meeting and held the office up to his election as President at the 1957 meeting. It was in this sphere of activities as Secretary-Treasurer and President of the Academy that Webster displayed his talents. He was one of those gifted men, the chosen few, who was caught up completely—yes, burned up, too—in his work. Those of us who knew him well know how he gave of himself so unselfishly and so unstintingly at great personal sacrifice that American dermatology might grow and prosper, and he did all this at what we now know and always knew was his own great personal sacrifice. He was at the beck and call of each of us whenever and wherever he was needed.

Dr. Webster was not a prolific writer. However, his more than twenty published papers clearly illustrate his vast dermatologic knowledge and his clear and orderly thinking. He was an excellent teacher and was admired and respected by undergraduate and graduate students.

May I say now that perhaps the most significant source of his inspiration was his family, his beloved Ruth and his two sons. I have no right to enter into the sacred intimacy of this reservoir of his strength. But even a stranger could see that there was entire rapport between his work and his family. There was no conflict here—no feeling that in pursuing his work with such relentless zeal and vision he was denying them. His ideals were theirs. His work was their work. Let his work be their most comforting memorial. For a number of years, the physical strength of Dr. Webster was ebbing. His emphysema became progressively worse, and yet in spite of this physical disability, his mind was clearer than ever and his devotion to the Academy greater than ever. Perhaps this can be explained by the following quotation from "The Guide to the Perplexed": "When the perfect man is near death, his knowledge increases mightily and his love for the object of his knowledge becomes more intense and it is in this great delight that his soul separates from his body."

Of many it is said that they were truly religious, but this is too generalized a phrase for Jim. He had a sense of God and ethical principles in all his undertakings and a belief that these must be expressed in his work and in his daily living. And now James Randolph Webster has taken his place in Eternity. May the remembrance of him be ever cherished by those who knew him and had the privilege of working with him. For the greatest attainment a man can have is neither a statue, nor the publication of his works, nor even a place in history books. The greatest monument is left in the hearts of those who knew him and worked with him. And all of us who have known Jim Webster and were privileged to call ourselves his friends will agree that merely to have known him was an experience that will forever remain one of the greatest treasures of our lives.

S. J. Zakon
Chicago

The New, Newer, and Newest

Rumor has it that Summit Conferences are being held with a view to combining somehow the Annual Meeting of the Society of Investigative Dermatology and the Section on Dermatology of the American Medical Association—each society to retain its identity and its publication. Good move, good luck!!

Allan Lorincz, in a discussion before the Illinois State Medical Society in May, "speculated wildly," in view of the key psychopharmacologic roles played by tryptophan metabolites, on the possibility that the popularly assumed volatility and temperamentality of redheads may in some way be related to the way they metabolize tryptophan. Think of it—it's been chemistry all the time.

Honors

William Dobes, who has just completed his term as Chairman of the Southeastern Dermatological Association, was honored by election to Commodore of the Atlantic Yacht Club, one of the outstanding clubs of its kind, winner of several important national and international regattas.

Ernest Strakosch and I were elected Corresponding Members of the Austrian Dermatological Society, and Francesco Ronchese is now a Corresponding Member of the Dermatological Society of Uruguay.

Marion Sulzberger was elected an Honorary Member of the French and Israeli Dermatological Societies. He is also President of the International League of Dermatological Societies. Incidentally, for some unknown reason, there have been many inquiries concerning Sulzberger's health. He reports that his health is excellent and his mental state is the "same as it has always been, insofar as I can judge."

At the 10th annual meeting of the Pacific Dermatological Association, to be held in Coronado, Calif., Sept. 18 to 20, 1958, there will be speakers from fourteen different universities. Among the dermatologist-guests will be George Andrews, James Burks, J. Lewis Pipkin, Leonard Weber, and, from Mexico, Fernando Latapi. The nondermatologists from the fields of radiation, cancer, and plastic surgery are Frederick Mohs, Vincent di Raimondo, Paul Pierce Pickering, Bernard J. O'Laughlin, Amos Norman, and Moses Greenfield. Max Obermayer, Victor Newcomer, Murray Zimmerman, Kenneth Baker, and Ervin Epstein will represent the local talent, and there will, as usual, be a clinical meeting, round-table discussions, and panels on histopathology and therapy, made up seemingly of practically the entire membership of the Pacific Dermatological Association. All dermatologists are invited—for a "small registration fee," according to Louie Weiner, Secretary.

Attention Kansas City Area dermatologists: We note that the Kansas City South East Clinical Society will have among its speakers, Sept. 22, a pediatrician to discuss Common Skin Disorders in Infancy and Childhood. Tsk! Tsk!

The new officers of the Detroit Dermatological Society are George Sexton, of London, Ont., Canada, President, and Alice E. Palmer, of Detroit, Secretary. The Philadelphia Dermatological Society has elected Herman Beerman President for the second time; the first was in 1940. And The Southeastern Dermatological Association has elected Barrett Kennedy, Chairman, and Harry Robinson, Secretary.

Comforting Bits of Information

If you find it difficult to remember events, even yesterday's events, you should have no cause for concern—it's normal, according to Dr. Lewis J. Sherman, of the Veterans' Administration.

Just in case you should be contemplating travel in space, the bank of extremely intense radiation surrounding the earth at a distance of 600 to some thousands of miles does not pose a threat of quick death, according to Dr. H. M. Pratt, of Argonne National Laboratories.

Total prevention is the best treatment of arsenic poisoning in children, according to the New York City Department of Health, and "Res-Q" is the inspired name for a universal antidote for accidental poisonings; it contains activated charcoal, magnesium hydroxide, and tannic acid.

H. R.

Society Transactions

CHICAGO DERMATOLOGICAL SOCIETY

Adolph Rostenberg Jr., M.D., President
Samuel M. Bluefarb, M.D., Secretary

Oct. 16, 1957

Unilateral Acrodermatitis Chronica Atrophicans.

Presented by Dr. Stephen Rothman.

A 52-year-old priest, born in Lithuania, noticed some color change of his right knee several years ago. About the same time he observed that his right leg was more susceptible to sunburn than his left. Since September, 1955, red and bluish-red patches have developed on right leg and foot. Some of these patches broke down and healed again. There had been some swelling of this leg from time to time. Subjectively, the patient experienced some strange sensations in the right leg, particularly in warm weather.

In the past the patient was treated with sodium cacodylate injections, with dressings for varicose veins, with Antergan pills and more recently with highly concentrated wheat-germ oil capsules (Denamone). The last treatment seemingly has brought about some improvement.

The patient displays typical changes of acrodermatitis chronica atrophicans with tissue-paper atrophy on knee and dorsum of foot. Both knees display hyperkeratosis due to pressure from kneeling. Nail of right big toe is dystrophic after an old trauma.

Physical examination was essentially normal. Abnormal laboratory findings were high plasma globulin (albumin 4.5 gm. % globulin 3.0 gm. %) and sedimentation rate of 23 mm. in one hour.

Discussion

Dr. S. J. Zakon: Dr. Rothman is correct in stating many times that acrodermatitis chronica atrophicans was more prevalent in the Austro-Hungarian Empire. This probably is also true for eastern Europe. This patient is a Lithuanian. The disease is comparatively rare in the male, and the unilateral type is also not common. This is a classical case of unilateral acrodermatitis chronica-atrophicans in the male.

Dr. Stephan Epstein, Marshfield, Wis.: I should like to ask a question. It has been reported that acrodermatitis responds well to penicillin. I wonder if anyone here is using this treatment and whether anyone also has experience with this treatment in scleroderma.

Dr. Bernard Yaffee: It does not work.

Dr. Stephen Rothman: As to Dr. Zakon's remarks on the frequency of this disease in the defunct Austro-Hungarian Empire, it is indeed remarkable that the disease is virtually never seen in American-born persons. This observation strengthens the belief that acrodermatitis of Herxheimer is caused by a specific organism or has a specific vector (tick?) which does not occur in this country. We could confirm the observation that penicillin is effective in combating the inflammatory component of the disease. In this case only wheat-germ oil was used as a therapeutic agent, as recommended by the referring physician, Dr. Paul Gross, of Columbia University.

As to the great effectiveness of chloroquine in the treatment of benign lymphocytomas, we saw amazingly fast resolution of such a tumor in a patient shown here several months ago. However, the patient developed corneal edema with this medication; the treatment had to be discontinued, and the lesion recurred.

Solid Edema. Presented by Dr. Milton Robin.

This 21-year-old man was in good health until June, 1955, when he discovered an asymptomatic swelling of the right lower eyelid. Within a period of several months the edema increased in severity, and then, for the first time, the patient visited his family physician. He was given penicillin and hot packs, with no amelioration of his symptoms.

In August, 1956, the patient was examined in an ear, nose, and throat hospital because of the persistence of the same asymptomatic edema of the right lower lid. According to the patient, he was told that a lipoma was present in the right cheek and that surgical removal might improve his condition. Surgery was performed during the same month—the route of removal of the tumor was through the buccal mucosa. After surgery, edema and swelling were noted for the first time on the left lower lid. No improvement was noted in the area of the right lower lid.

Submitted for publication Feb. 25, 1958.

In December, 1956, the patient was hospitalized a second time. On this occasion a skin section was taken from the edematous areas of the right lower eyelid and a muscle section, from his right thigh. Microscopic examination of muscle was normal, and examination of skin revealed edema, vasodilatation, and perivascular infiltration of superficial vessels of the corium. The epidermis was normal.

Physical findings are as follows: 1. Edema of both upper and lower lids, glabella, and adjacent cheeks. At times the degree of edema has fluctuated, but the edema has never disappeared. At no time have acute or subacute inflammatory changes ushered in or accompanied the edematous state.

2. Bulbous swelling of nose. Comedones, milium bodies, and acne papules on sides of nose. Patient states that since onset of his acne lesions he has picked and squeezed incessantly.

3. Skin adjacent to the nose and eyelids is firm to touch.

Laboratory findings were as follows: Urine was normal. Blood: Red cells 5,500,000, white cells 6500, sedimentation rate normal. Blood chemistry: October, 1956: nonprotein nitrogen 43.2 mg. %; November, 1956: nonprotein nitrogen 48.6 mg. %; December, 1956: nonprotein nitrogen 42.2 mg. %; January, 1957: serum urea 26.5 mg. %; April, 1957: nonprotein nitrogen 56.4 mg. %; October, 1957: creatinine 0.9 mg. %. Test for lupus erythematosus cells was negative.

X-rays of lungs, cardiovascular system, urological system, and bony systems were within normal limits.

Results of treatment were as follows: There was no improvement with antibiotics, internal and external; superficial x-rays, 7 quarter-units to lids and nose; allergic management; 1% Neo-Cortef Ointment and 0.1% Florinef lotion; antihistamines, or low-fat and low-cholesterol diet.

When steroids were administered by mouth, there was a lessening in the amount of edema, but the skin never took on a normal appearance. Edema promptly returned when the steroids were stopped. Four local injections of Cortril reduced the swelling of the lids temporarily.

Discussion

DR. FRANCIS E. SENEAR†: We showed a case a year ago in which the diagnosis was under question. The patient was a young woman who had been in the hands of internists for some time without any diagnosis being made. All types of investigation were carried out, with negative results. When I saw her I suggested solid edema as a possible diagnosis. Dr. Rothman saw the case and made some suggestions, and she did make some improvement. I ran across her in a store the other day. She was wearing glasses, and she took them off to show me that she still had the swelling, though it was less in intensity.

DR. MILTON ROBIN: The internist who referred the case was interested in knowing whether this was a part of a systemic process, because the patient had a steadily elevated red cell count. He thought that it was polycythemia vera. It is possible that there was some injury to the blood vessels of the face.

The other problem is as follows: Was there any significance to the progressive rise in the nonprotein nitrogen and serum urea nitrogen? It started with a normal high level of 42 mg. % and is now up to 56 mg. %.

When I presented this patient at the University of Illinois, we discussed the case as we have here and some came to the conclusion that we should refer the patient for boiling-water treatment. We have heard reports that persons have received benefit from this therapy, but, when it comes down to solidly discussing the indications and possibilities of this type of treatment, most of the information is vague and indefinite. If this discussion can be reopened, I should appreciate Dr. Brunsting discussing his experience with this form of therapy.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: In the absence of inflammatory reaction or a history of episodes of lymphangitis, this condition must be considered to be a case of solid edema of the face. If infection can be demonstrated, the use of sulfonamides, antibiotics, or perhaps a vaccine may be indicated. In general, I would prefer conservative treatment to the face, including perhaps, the use of roentgen therapy, but not a radical procedure such as the injection of boiling water into the tissues.

DR. HENRY E. MICHELSON, Minneapolis: It was stated in the history that the patient had had a lipoma removed from her cheek. When I was going over the literature on conditions of fatty tissue I ran into a number of reports in which cases diagnosed as solid edema on biopsy proved to be peculiar hypertrophies of the fat. It is just a possibility.

DR. MILTON ROBIN: I have injected hydrocortisone into both lids on four occasions, starting with 0.25 cc. and going up to 0.5 cc. There was definite improvement while the drug was used. After the drug was stopped there was a return of the edema. I injected hyaluronidase on one occasion and observed a diminution of the edema for a period of three days.

† Dr. Senear died Feb. 11, 1958.

Tuberculoid Leprosy. Presented by Drs. Irene Neuhauser and (by invitation) Roland S. Medansky and George Fleming.

This is the case of a 51-year-old white man who was born in Camagüey, Cuba, and lived there until one year ago, when he came to Chicago. Just prior to entering the United States he experienced a "feeling of hardness" in the right calf. No lesions were present at this time. His mother is living, aged 86, and his father died at age 81. Nine siblings are all in good health.

The lesion was first noticed in March, 1957. The lesion is annular and is approximately 5 in. in diameter, indurated, with a reddish infiltrate and a dry branny scale. The lesion is located on the right calf, and there is anesthesia within the lesion, but no systemic symptoms are present. The center of the lesion appeared hypopigmented. The right ulnar nerve appeared to be more palpable than the left but only slightly enlarged. The lepromin test, read within thirteen weeks, was positive in one-half normal dose (0.05 cc.). The test response consisted of a papule 1 cm. in diameter, which was elevated.

He has been taking Diasone, 0.3 gm. daily, from July 22 to Aug. 29 and from Sept. 5 to Oct. 12.

He states that the lesion has become soft, and it is now much lighter.

The histopathological report was as follows: Histologic sections from the patch of eruption on the right lower leg revealed the essential pathologic alterations in the corium. Here we see discrete tubercles consisting of epithelioid cells and Langhan's giant cells surrounded by lymphocytes. In one of the larger tubercles caseation necrosis is evident. Most of the tubercles surround blood vessels and sweat glands, but a few tend to invade the pilomotor muscles. A Ziehl-Neelsen stain revealed an occasional acid-fast bacillus.

Lepromatous Leprosy. Presented by Drs. James R. Webster and Stanley Huff and (by invitation) J. Latoni.

This 38-year-old Mexican woman states that for the past three months she has noticed "some spots" on her lower extremities followed by lesions on her face, ear lobes, and upper extremities. She states that she had similar lesions 12 years ago which faded in 6 months.

Three months ago a local physician discovered the presence of Mycobacterium leprae on a nasal smear. The patient was referred to the Health Department and, later to Cook County Hospital. Her husband died seven years ago of carcinoma of the lung.

Her parents, sister, and daughters were examined, and no evidence of the disease was present.

This patient presents a disseminated dermatosis of the face, ear lobes, and extremities, symmetrical and monomorphous, consisting of round firm reddish infiltrated nodules of various sizes, irregular in shape, some coalescing in patches. A small nodule was removed from the conjunctiva for histologic study. Some hypesthesia is present. The lesions are nontender. There is generalized adenopathy. The mouth mucosa is slightly hyperemic.

Laboratory findings were as follows: Tuberculin test was positive 1:10,000; lepromin test was negative in three weeks; abnormal bone marrow was found, with positive acid-fast stains. Blood chemistry showed nonprotein nitrogen 34 mg. %, chloride 102.0 mg. %, sodium 139 mg. %, and potassium 3.8 mg. %. The kidney, ureter, and bladder were normal. The Kahn reaction was doubtful, and the Wassermann reaction, negative. The urine was normal. Scrapings from the ear lobes were positive for acid-fast bacilli. Complete blood cell count showed hemoglobin 58%; red cells 4,580,000; platelets normal; white cells 6600, with lymphocytes 16% and monocytes 8%.

Diasone was given for treatment. (Biopsy specimen is presented.)

Discussion on Preceding Two Cases

Dr. Norman Tobias, St. Louis: Both of these cases are classical examples of leprosy. The woman with the lepromatous type of lesion has an extensive type of leprosy, and the biopsy specimen showed typical Mycobacterium leprae. I observed over 200 cases of leprosy in Hong Kong this summer. I was surprised at how many early cases came to the clinic. One of the early symptoms was numbness. A number of patients came in with solitary lesions that looked like psoriasiform plaques and which I would never take for leprosy. Although there are many cases of leprosy with orthopedic complications, there are too few plastic surgeons to take care of these patients. Diasone is used at St. Andrew's Dispensary, where most of the lepers are treated. Lepers are not treated on the same day as the skin patients, for psychological reasons. I was surprised at how many of these Chinese patients diagnose leprosy themselves and come in voluntarily.

Dr. Leon Goldman, Cincinnati: These cases showed also very striking differences in the lepromin reaction. The woman has several children and claims they were examined for leprosy. How they were examined we do not know. It is very difficult for us to diagnose clinically early leprosy in children because results of tests of the skin may be negative or the lesions may show merely faint bluish pernio-like areas on the arms. A biopsy should be made in children; also the lepromin test should be done. With her lepromatous form, she is infectious.

It is interesting to study the histamine test on normal skin and in the lesion, the electrical resistance, and the effect of local nicotine injections in the patient with the tuberculoid type. These tests show objective differences between the anesthetic and the normal skin.

DR. SILAS WALLK: The biopsy specimens of multiple lesions all showed the classical changes which we see in lepromatous leprosy.

DR. IRENE NEUHAUSER: I do not know the incubation period of leprosy. I do know that leprosy has been reported in a child of less than one year of age, and other patients have developed clinical leprosy many years after the believed exposure.

I disagree that the patient at Cook County Hospital has a classical lepromatous leprosy. At the 1953 International Congress, in Madrid, the classification committee recognized two distinct types of leprosy: the tuberculoid, representing a high degree of response, and the lepromatous, with complete lack of response. Between these two extremes there must be many degrees of response or lack of response. To the two types of leprosy, two groups were added. These groups have less distinct characteristics, less stability, and less certainty with respect to evolution. These groups consist of the indeterminate group, previously recognized, and the borderline, or dimorphous, group. The dimorphous form is usually strongly positive on bacteriological examination, and the nasal mucosa is usually negative. I noticed that the nasal findings in this patient were positive, but I wonder whether the identity of the organism was verified. There was some infiltration in the ear lobes but none in the outer portion of the eyebrows. The lesions on the patient's face were soft, shiny, and poorly defined. The Wassermann reaction was negative.

Leprosy is classified on the basis of the clinical picture, bacteriological and immunological findings, and histopathology. The section shown today was typical of lepromatous leprosy, but I am told that some sections were typical of indeterminate leprosy, which is a characteristic of the dimorphous form.

The patient's rapid response to treatment is another argument in favor of a more benign form. Recently several interesting papers have been published on the follow-up of lepromatous patients undergoing treatment. As these patients have improved they have gradually presented the characteristics of dimorphous leprosy.

The patient whom I presented has a typical tuberculoid leprosy showing asymmetry of nerve involvement and a sharply outlined, smooth, dry lesion with loss of cutaneous sensibility.

Case for Diagnosis: Pemphigus? Presented by DR. DOROTHY B. WINDHORST (by invitation).

A 27-year-old bottle salesman first noted the appearance of the presenting skin lesions some two to two and one-half years ago. They first appeared over the left ear and in the scalp and then on the chest. There is also one penile lesion. All lesions have remained symptomatic. The patient cannot recall seeing any lesions clear or become smaller, although the scaling has been controlled to some extent by various ointments. He has never noted blister formation. He has seen several dermatologists and has received ointments (including Pragmatar), x-ray treatment, and ultraviolet-light therapy. Except for his skin lesions, the patient's general health has been excellent.

The lesions are circular, erythematous, sharply limited, macular patches having a sharp border and no tendency to become confluent. The color has varied from a bright angry red to a paler pink on occasion. There is a variable type of scaling present on these patches. The scalp lesions tend to have crumbling, greasy, piled-up scales which can be brushed out and are profuse enough to be a cosmetic annoyance. Other patches have thin, white, adherent scales; one of these on removal showed "carpet tacking" suggestive of follicular plugging. No atrophy, telangiectasia, or other evidence of follicular plugging has been noted. There are a few small pits on one fingernail.

The remainder of the physical examination is negative. Laboratory data are as follows: hemoglobin 16.3 gm., white blood cells 8100, serological tests negative, urine normal.

The histologic report was as follows: Five biopsy specimens were taken. One from a chest lesion (No. 930) shows suprabasilar clefting, acantholysis, and dyskeratotic cells with widespread parakeratosis and acanthosis and some edema of the epidermis. A section from the scalp (No. 994) shows considerable epidermal edema and vacuolated cells with lost prickles. Two sections from chest and scalp (No. 964 and No. 996) show a psoriasiform picture (fairly regular acanthosis, parakeratosis, and dilatation of papillary capillaries but also patchy indistinctness of the granular layer). A specimen taken recently (No. 994) also shows acantholysis.

Discussion

DR. FRANCIS E. SENEAR: I saw this patient and thought that this was an extremely interesting case and a very difficult one from a diagnostic standpoint. Dr. Rothman asked me to look at it, particularly because he had the diagnosis pemphigus erythematosus in mind. You will recall from the history that was presented today that acan-

tholysis was found on two occasions. It is my understanding that you can find acantholysis in some patients who are not in the pemphigus group. There is so much confusion about the whole group and so much lack of unanimity with regard to the pathologic elements in the diagnosis that I certainly would not on that basis make a diagnosis of pemphigus erythematosus. I do not think that Dr. Rothman believed that this belonged in the pemphigus group. However, I think that this is a very good possibility in view of the types of involvement on the scalp and on the chest. But with the long duration of the condition without any change, which, of course, is not impossible with pemphigus erythematosus, I would anticipate that ordinarily by this time he would have shown some other changes of pemphigus. Otherwise, I would not know where to place it except in some of the seborrheic types. As you all know, the French speak of these as seborrheic pemphigus rather than pemphigus erythematosus, because in their experience, as well as in some other places, most of the patients start with a condition which is essentially seborrheic in character. This has not been the experience generally in this country. If it is not pemphigus erythematosus, and I do not think it is, we shall have to regard it as seborrheic dermatitis.

DR. F. J. SZYMANSKI: The protocol mentioned of five biopsies. I was able to find the slides from only four biopsies. In two the changes were consistent with a diagnosis of psoriasis. However, in the third the changes were certainly not diagnostic but were consistent with a diagnosis of superficial epithelioma in situ. The fourth slide showed changes that resembled Hailey and Hailey's disease. I admit I am confused, but occasionally acantholysis is observed in a Bowenoid epithelioma. Could this be a case of psoriasis associated with superficial carcinoma in situ?

DR. STEPHEN ROTHMAN: Pronounced acantholysis in two of the five specimens hardly can be interpreted as an incidental finding. I am inclined to believe that this is either a case of Senear-Usher syndrome or a very unusual type of Darier's disease. This patient was treated for psoriasis by experienced dermatologists, but antipsoriatic treatment had not the slightest effect on the lesions.

DR. F. J. SZYMANSKI: The condition that was described as isolated Darier's disease is actually a wart-like tumor, and it is not an erythematous psoriasiform plaque.

DR. DAVID W. KERSTING, Milwaukee: Having also noticed in some of these many biopsy specimens a pronounced cellular disarrangement in epidermis, pleomorphism of squamous cells, and bizarre nuclear chromatin in some of the squamous cells, I agree emphatically that this corresponds to a so-called premalignant dermatosis on the order of Bowen's disease, early stage.

DR. A. H. SLEPYAN: You will recall that several months ago I presented a man with a most peculiar psoriasiform eruption of the palm and wrist of one hand. In this case four or five biopsies were performed before a diagnosis was possible. On the last section we found an unusual exaggeration of the epidermis, with many cells that looked much like Paget's cells arranged in their peculiar basket-like groupings. On clinical grounds alone we thought strongly of an atypical psoriasis or a peculiar type of mycosis fungoides. The microscopic picture has repeatedly proven this to be an epithelioma.

DR. DOROTHY B. WINDHORST (by invitation): The discussion is really an extension, and a very gratifying one, of what has been going on in our department for the past two weeks. One thing that was brought out was the possibility of preepitheliomatous lesion. We will certainly give this due evaluation. Our primary diagnosis has been pemphigus erythematosus rather than psoriasis.

Case for Diagnosis: Discoid Lupus Erythematosus; Polymorphic Light Eruption? Presented by DRS. S. M. BLUEFARB and (by invitation) J. HASEGAWA and F. LEVIT.

This 63-year-old gardener first noticed his skin trouble in May, 1957. Red scaling lesions appeared on his left temple and gradually spread to involve most of the face, then the hands and arms. He saw a dermatologist, who treated him with Atabrine and lotions, but the condition progressed in spite of treatment.

On admission to Veterans' Administration Research Hospital on July 22, 1957, the patient's general physical condition was within the normal range. His dermatitis involved the face, the V of the neck, the hands, the forearms, and the arms and had fairly sharp demarcation at the borders. There were many small and large flat, erythematous, scaling lesions, most of which were confluent.

Laboratory findings were as follows: The white cell count was 5250 on admission but later ranged from 6000 to 11,000; hemoglobin was 16.4 gm. %. Urine was negative except for occasional white and red blood cells. Total protein was 7.73 gm. %, with albumin 5.8 gm. % and globulin 1.86 gm. %; urea nitrogen was 19.0 mg. % and fasting blood sugar 112 mg. %. VDRL was negative on two occasions. Urinary porphyrins were negative. No lupus erythematosus cells were found on five examinations. CRP was negative. ASO titer was 40 Todd units. The electrocardiogram was within normal limits, except for sinus bradycardia.

Exposure of a small area of skin to a therapeutic ultraviolet unit for approximately one

erythema dose resulted in no remarkable reaction. Several exposures of one extremity to suberythema ultraviolet have resulted in no detachable change in that extremity.

The patient has been treated with chloroquine, initially 750 mg. daily and now 500 mg daily. There has been little or no change in his clinical appearance since admission.

Slides of biopsy specimens removed on admission and two months later are presented.

Case for Diagnosis: Lupus Erythematosus; Verrucous Nevus? Presented by DR. BRUCE BAIRSTOW (by invitation).

Approximately June 25, 1957, a 5-year-old girl had what was apparently a scratch on the side of her nose. Prior to that time her skin was absolutely clear and she had no story of any previous skin disease. The eczematous-appearing initial scratch spread to involve her face, ears, and occiput without any hair loss. She was seen by a doctor in Michigan, while on vacation, and he prescribed what was apparently Neo-Cortef, which seemed to help the eruption. She subsequently saw another doctor, who prescribed calamine lotion, which apparently did not help.

When first seen the eruption was eczematous in appearance, and within a week it had assumed the verrucous aspect that it now presents.

In addition to the verrucous lesions on the face and ears, at the present time she has scaling erythematous patches on her scalp and a poikilodermatous appearance on her neck and upper arms. Therapy has consisted of vitamin A, 50,000 units daily, and 5% salicylic acid ointment. For the past month she has been taking Aralen, 125 mg. daily. Biopsy was performed, and the specimen is shown today.

Her past history included measles, appendectomy, and roseola.

Discussion on Preceding Two Cases

DR. H. E. MICHELSON, Minneapolis: I considered three possibilities in the first case aside from polymorphic light sensitization: lupus erythematosus, lichen planus, and psoriasis. I have seen a number of patients with a similar condition, and the microscopic examination permitted a diagnosis of psoriasis. One must keep in mind that in people of his age, 67, the skin is atrophic and there is a minimal amount of scaling.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I agree with Dr. Michelson's diagnosis of incontinentia pigmenti in the child. This is a very interesting case. It originated as a red line which the mother thought was a scratch, but there is no history of injury. Later on, verrucous lesions and pigmentation occurred, and there was also pigmentation in areas without previous skin involvement. The combination of verrucosities and a peculiar, nevus-like pigmentation with a lesion of the scalp with partial alopecia strongly suggests an abortive case of incontinentia pigmenti. Blisters were not present, but they are not necessary for the diagnosis of this condition. Most unusual is the delayed onset at the age of 4 years. Incontinentia pigmenti usually occurs at or shortly after birth. However, the two cases of Nägeli originated at the age of 2 years.

DR. HAROLD SHELLOW: I should like to speak about Dr. Bluefarb's case. I was struck by the fact that there has been relatively little sun that this man has been exposed to in the past month and yet his eruption has remained stationary. He said that he had no eruption elsewhere on the body and none on the legs. However, on the legs I found lesions that were more or less coalesced and had some micaceous scaling. I removed a little with my fingernail and thought I saw an Auspitz sign. I thought that the lesions on the legs were psoriasiform, those that occur in elderly people when they develop psoriasis later in life. Several of the nails showed dimpling and pitting. I think that this man has psoriasis.

DR. DAVID W. KERSTING, Milwaukee: As I looked at the skin lesions of the child presented by Dr. Bairstow I suspected incontinentia pigmenti. Studying the sections, I was not able to exclude it. I wonder whether Dr. Becker thought that the histologic detail of these pigmented lesions supported an impression of incontinentia pigmenti.

DR. S. W. BECKER JR.: I do not think that the histology of incontinentia pigmenti is specific at any one stage. The findings in this patient are compatible with incontinentia pigmenti.

DR. J. HASEGAWA (by invitation): I should like to thank those who took part in the discussion. The question of psoriasis was brought up also in this man's hospital stay. We had tried various things without response. After consideration of the histologic sections the diagnosis was unlikely.

DR. S. M. BLUEFARB: There was one feature in this case which led us to believe that this patient had lupus erythematosus rather than psoriasis. This opinion was based on the response to therapy with Aralen. It has been noted that the administration of Aralen to patients having psoriasis will invariably result in an increased severity of the condition, and, in some cases, an exfoliative dermatitis develops. This reaction is probably due to interference with an enzyme system, since all of the patients with this reaction whom we have studied evidenced a deficiency of vitamin B. Our patient showed some improvement while taking Aralen therapy.

DR. BRUCE BAIRSTOW, Waukegan, Ill. (by invitation): When I first saw this child, she had

considerable vesiculation, not radically different from the appearance in eczema. As this picture cleared, she developed the verrucous picture that you see today. She has even improved in the past three weeks according to comparisons of photographs I took then with her appearance today. The biopsy showed on one occasion the appearance consistent with lupus erythematosus and on another section was thought to be compatible with verrucous nevus. The question of Nägeli type of incontinentia pigmenti arose.

She has always been in good health and has shown no systemic difficulties that have been discovered by her pediatrician.

Systemic Blastomycosis. Presented by Drs. Allan L. Lorincz and (by invitation) William Gillespie (referral of Drs. Frank J. Kendrick and Sylvia F. Griem, Gary, Ind.).

Discussion

Dr. Leon Goldman, Cincinnati: This is a man of middle age with lesions that look clinically like blastomycosis. There is a draining sinus that looks like a tuberculous sinus.

As far as the immunobiology is concerned, we have had patients who have had negative or positive blastomycin tests. We have had some with negative complement-fixation tests and some with positive complement-fixation tests. For prognosis we would depend rather on the clinical state and biopsy sections showing the organisms. The number of organisms, their size, and the "tissue response," are some factors to be learned from a study of the biopsy specimen.

I should like to say something about the new treatment for blastomycosis, that is, use of amphotericin B intravenously. This is helping patients with visceral histoplasmosis, torulosis, and blastomycosis. In our experience, the response in blastomycosis is more rapid and so far more sustained than with the stilbamidines. In the cases we have seen, the improvement was striking. Dr. Jan Schwarz, in his experimental work in Cincinnati, has found it is the only drug that has cured experimental histoplasmosis in animals.

Dr. F. J. Szymanski: As an aid in trying to find the organisms of blastomycosis in sections from such cases we have been using a methenamine silver nitrate stain, and we find it more beneficial than the Schiff-McManus stain. The organisms pick up some of the silver, with the result that there is greater contrast between the fungi and the cellular background. The task of finding the Blastomyces organisms becomes much simpler with the methenamine silver nitrate method.

Sarcoidosis. Presented by Dr. Otto C. Stegmaier, Davenport, Iowa.

Sarcoidosis. Presented by Drs. James R. Webster and Stanley Huff and (by invitation) Martin L. Gecht.

Discussion on Preceding Two Cases

Dr. Henry E. Michelson, Minneapolis: Dr. Stegmaier asked for some suggestions on therapy. It has been my view that patients with sarcoidosis should not receive steroid therapy unless there is some organ or systemic difficulty that is dangerous enough to warrant the use of those remedies. As you know, the steroids do not cure sarcoidosis, even though they cause the lesions to temporarily disappear.

Dr. Adolph Rostenberg Jr.: I should like to go on record as agreeing with Dr. Michelson concerning treatment of patients with sarcoidosis. The mere fact that a patient has sarcoidosis is not by itself a reason for therapy. The presence of skin lesions, with no evidence of visceral involvement, does not mean that he should be treated. If the patient has involvement of the eye or symptoms in other viscera referable to his sarcoidosis, then he should be treated. One reason for going slowly with steroid therapy is that there is also the possibility of a mistake in diagnosis. There is no question that cases of tuberculosis are labeled as sarcoidosis, and there steroids will harm.

Urticaria Pigmentosa Bullosa. Presented by Drs. Clark W. Finnerul and Frederick J. Szymanski.

Discussion

Dr. Isadore Fisher, Minneapolis: At a recent meeting in Winnipeg, Manitoba, Canada, two infants with urticaria pigmentosa bullosa were shown. In both of these cases after stimulation the lesions presented a peculiar flushing that was likened to a serotonin reaction. This is something to think of in future cases.

Dr. Stephen Rothman: I believe that there is a well-defined group in which the involvement is purely cutaneous. I have followed three patients for decades. As they grew older they had less and less trouble with urticaria and itching, but the pigmented spots have remained unchanged. One of these patients is now 68 years old and is perfectly healthy otherwise.

Melanin Hyperpigmentation (Adrenocortical Insufficiency?). Presented by Drs. Stephen Rothman and (by invitation) Robert C. Ranquist and Richard L. Landau.

A 49-year-old white teacher noticed early in 1957 darkening of her skin, mainly on the outer surfaces of her arms. She experienced no fatigue, weight loss, or malaise. She has no history of excessive sun exposures. In the summer of 1956,

she took "hormone pills" for menopausal symptoms. At the same time she used "Skol" locally against sunburn. Otherwise, she did not take any drugs and did not use any local applications.

There is diffuse hyperpigmentation with tiny interspersed nonpigmented areas on the neck, arms, and hands and more on extensor surfaces, on hips, and around the ankles. Axillary hair is absent; pubic hair is sparse.

Biopsy sections are presented and show melanin hyperpigmentation and absence of iron pigment.

Laboratory data are as follows: Serum sodium 131 and 128 mEq. per liter (normal 135 to 145), serum chloride 97.0 mEq. per liter (normal 99 to 108), serum potassium 4.7 and 4.4 mEq. per liter (normal 3.5 to 5.0). Urine negative, white blood cell count 5700, hemoglobin 14.8 gm. Differential count: 58% polymorphonuclear cells, 35% small lymphocytes, 4% monocytes, 3% eosinophils. Sedimentation rate was 27 mm. in one hour; Kahn test was nonreactive.

The patient was studied by Dr. Richard L. Landau, of the Endocrinology Clinic, and his report is as follows: The pigmentation and perhaps the lack of axillary hair suggest the possibility of adrenocortical insufficiency. However, other purely clinical considerations militate against this diagnosis. Primarily, she feels very well. Although she is thin, there has been no weight loss. Her appetite is good. There have been no characteristic abdominal or gastrointestinal symptoms. She stoutly maintained that her energy level was unimpaired. On physical examination her blood pressure was 140/70 with no postural change; the absence of a postural drop is additional evidence against Addison's disease.

On the other hand, the laboratory findings, while not diagnostic, also tend to suggest the possibility of an adrenal defect. After drinking 960 cc. of water, she voided just 265 cc. A more normal response would have been 700 to 1000 cc. While all untreated patients with Addison's disease fail to diurese after a water load, there are other conditions in which one may see such a result (notably debilitated state, renal disease).

The low serum sodium value is also suggestive of adrenal deficiency but, like the positive Kepler test, is seen in other states as well. The absence of an elevated serum potassium would not be anticipated in Addison's disease.

This diagnostic dilemma might be resolved by the performance of urinary corticoid assays and an ACTH test. These we will do.

Discussion

DR. S. W. BECKER JR.: It is likely that this hyperpigmentation is due to a decrease in adrenal activity with an elevation of the melanin-stimulating hormone. I think it would be interesting if the melanin-stimulating hormone level could be determined.

Pustular Trichophyton Rubrum Infection of the Scalp with Scarring and Permanent Alopecia.
Presented by DR. IRENE NEUHAUSER.

DR. STEPHEN ROTHMAN: I wonder about the mental development of this child. She has behaved rather as if she is retarded. It is a peculiar fact and poorly understood that retarded children have the severest and most intractable forms of dermatomycoses.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: A recent report (A. M. A. ARCH. DERMAT. 76:252 [Aug.] 1957) indicates benefit in a long-standing case of Trichophyton rubrum infection following a series of intramuscular injections of γ-globulin. I have tried this in one instance recently without any benefit whatsoever.

DR. LEON GOLDMAN, Cincinnati: Dr. Albright emphasized background of glandular dysfunction in children with systemic mycoses. We have had several cases in the Children's Hospital with monilial infections but never with as massive a T. rubrum infection as this. The poor skin which is part of the deficient background is supposed to favor growth of the infection.

DR. J. J. SICKLEY: Have studies on the proteins been done for agammaglobulinemia?

DR. IRENE NEUHAUSER: In answer to Dr. Rothman's question, this patient is definitely subnormal. There seems to be little doubt that such infections occur more frequently in subnormal children. When this patient was first presented, it was agreed that she had congenital ichthyosiform erythroderma. A number of articles have been published describing extensive T. rubrum infections in persons with ectodermal anomalies. Baer, in 1947, published a very interesting article describing a patient with a generalized T. rubrum infection with nevoid changes in the skin, and several articles have been published of generalized infections with ichthyosis.

I am showing this patient today because of the scalp involvement. There is some controversy in the literature whether T. rubrum infections are endothrix or ectothrix infections. Some articles have been published showing photographs with endothrix involvement, and others, with ectothrix involvement.

I have examined many hairs from this patient and have found only an ectothrix type of involvement. This patient has an extensive infection of the skin, and the organisms seem to penetrate the hair follicle, causing complete destruction of the follicle.

In the ARCHIVES for April, 1957, Mullins and Watts reported a case of T. rubrum infection

with abscess formation. They found hyphae but no bacteria in the abscess. This patient has the same type of infection. Most reactions in the scalp are of the kerion type, with hypersensitivity and usually some secondary infection. This patient obviously has no hypersensitivity and has not responded to any therapy used.

In reference to Dr. Brunsting's suggestion, I have been considering γ-globulin therapy but first wish to do some electrophoretic studies to determine the amount of γ-globulin present.

Impetigo Herpetiformis? Presented by Drs. Theodore Cornbleet, Sidney Barsky and (by invitation) Martin L. Gecht.

This patient, a woman aged 30, first noted a pustule on the back of her neck in October, 1954, four weeks after childbirth. This began to spread peripherally, forming larger lesions, some of which became confluent. The centers of these were clear, but the borders were pustular, crusted, and arciform. They were similar to those seen on the chest and axilla at this time. During the first episode, the lesions were limited to the neck and popliteal areas. The exacerbations and remissions would usually last two to three weeks. Each recurrence would involve greater areas, and eventually, in May, 1957, the entire body excepting the palms, soles, and face developed lesions. During this period, she was treated with penicillin but did not respond. The patient was hospitalized between June 13 and July 8, and gradually the lesions resolved. New lesions did appear and were pustular from the start, never being vascular. Therapy consisted of rest, antihistamines (Di-Paralene), colloid baths, bacitracin ointment, and aluminum subacetate dressings. During the last week of her hospital stay, she received 1.0 gm. of Gantrisin q. i. d. The lesions seemed to heal more rapidly. She was discharged with no pustular lesions but was covered with postinflammatory hyperpigmentation where the lesions had been. The present exacerbation began Oct. 1, 1957. At no time has this patient demonstrated constitutional symptoms, such as fever or prostration. The patient stated that she missed her last menstrual period.

A group of cases clinically and histologically similar to this was described under the title "Subcorneal Pustular Dermatoses," in the December, 1956, issue of the *British Journal of Dermatology*.

Laboratory findings were as follows: Urine was normal. Complete blood cell count showed no abnormalities. Nonprotein nitrogen was 30 mg/100 cc.; glucose, 110 mg/100 cc. Serology was negative. Cultures of pustular material were as follows: first was sterile; second showed hemolytic Staphylococcus pyogenes var. aureus, coagulase-positive. Biopsy specimen showed intraepidermal pustule.

Discussion

Dr. Stephen Rothman: The clinical picture is compatible with the diagnosis of dermatitis herpetiformis.

Dr. Stanley Huff: This case resembles very closely the clinical and microscopic picture described by Sneddon and Wilkinson as subcorneal pustular dermatosis. They considered all these other possible diagnoses also, but none seemed to fit. Subsequent to their article there were a couple of cases reported by Hellier in which the possibility of the disease being a pustular bacterid was considered.

Dr. Theodore Cornbleet: This woman has myriads of matchhead-size pustules arranged in large circular sweeps and concentrically. Morphologically and because of an associated pregnancy there was the suggestion of impetigo herpetiformis. She is not ill, and so a major consideration is lacking to substantiate that diagnosis. We did not offer it seriously. The eruption has responded well in several days to a sulfonamide. The presence of a kind of impetigo (pyoderma) or a form of erythema multiforme is the most likeliest conclusion here.

Acquired Halo-Nevus-like Formation From Benoquin. Presented by Drs. Theodore Cornbleet and Sidney Barsky and (by invitation) J. Latoni.

This 45-year-old Negro woman states that she first noticed "spots" on her nose three years ago which gradually involved the whole face. Last year she applied "Palumos skin cream" for two months but stopped "because it made her sore." She was seen in our clinic last July, and Benoquin ointment was prescribed, with subsequent patchy hypopigmentation as seen today.

The patient presents a localized dermatosis involving the face and consisting of hypo- to hyperpigmented macular patches of varying intensity. On the left side of the chin a hypopigmented patch 1 cm. in diameter is present, at the center of which is a 2 mm. hyperpigmented macule (junction nevus?).

Discussion

Dr. S. W. Becker Jr.: This patient's history was a little vague. She had pigmentation on the face for three years and had used a proprietary ointment, presumably containing ammoniated mercury. After using this ointment she developed a dermatitis and was given Benoquin ointment. She used it for a week. According to the patient, whitish areas appeared on the face after a few days of therapy.

Ito (*Tohoku Journal of Experimental Medicine* [Supp. 5] 65:64-74 [May] 1957) has reported

this syndrome under the name of monobenzylether-hydroquinone leukomelanoderma. Patients usually stated that there had been a slight dermatitis when monobenzyl ether of hydroquinone ointment was first used. This sensitivity disappeared, and the patients continued using the ointment. After a varying time they developed hyperpigmentation, hyperpigmentation with small areas of depigmentation, or patchy areas of complete depigmentation. Some of this depigmentation was permanent. Microscopic examination revealed a reaction in the basal-cell layer and later the prickle-cell layer that apparently destroyed the pigment-forming cells.

Fortunately, this type of reaction is not common. Whenever a patient is using a monobenzyl ether of hydroquinone ointment, therapy should be stopped if the patient develops (1) dermatitis, (2) increased pigmentation, or (3) gray or bluish coloration indicating the formation of dermal pigment.

DR. THEODORE CORNBLEET: At Cook County Hospital we have seen some of these reactions that Dr. Becker mentioned. The induced leukoderma may be permanent, or a slate-graying may follow. I believe these permanent and disfiguring possibilities need emphasis, especially because they so often are permanent.

Perhaps Dr. Becker would want to include among the frequent untoward effects of Benoquin a post-inflammatory melanosis. The Negro, I found, finds these hyperpigmentations less objectionable than the vitiliginous changes. We thought that the latter were brought about by interference with the enzymatic oxidative melanin reaction. Dr. Becker's statement of actual destruction of the melanocytes is new to me. Some time ago we sought to learn if the central pigmented punctum of the halo nevus bore some relation to the surrounding depigmentation—some kind of restraining effect. By a punch biopsy we removed this centrum, but we were disappointed that this operation had no effect as far as darkening the hypopigmented periphery.

Hodgkin's Disease. Presented by DRS. SAMUEL M. BLUEFARB, SILAS WALLK, and (by invitation) HASSAM M. YAZDI.

Discussion

DR. SAMUEL M. BLUEFARB: Ulcerative cutaneous lesions of Hodgkin's disease have been described by Drs. Senear and Caro. They stated that three types of lesions occur: (1) cutaneous nodules which become ulcerated; (2) extensions of this process from a lymph node, bone, or other tissues, and (3) lesions in which the skin is the primary focus of the disease. This case appears to be one which can be included in the third group of lesions which occur in Hodgkin's disease.

Herpes Zoster Associated with Chronic Lymphatic Leukemia. Presented by DRS. DAVID V. OMENS and (by invitation) HAROLD D. OMENS and J. LATONI.

Discussion

DR. S. M. BLUEFARB: The numerous reports of the association of leukemia and herpes zoster appear to indicate that the occurrence of these two conditions is more than coincidental. In the reported cases, 103 patients had leukemia associated with herpes zoster and, of these, 79% had chronic lymphatic leukemia, 17% had granulocytic leukemia, 1% had monocytic leukemia, and the type was not given in six cases. However, this incidence is undoubtedly much higher, since only a minority of these cases are reported. The herpes zoster usually developed two or three years after the onset of the leukemia, but in rare instances the zoster was the initial symptom of the disease. In 37% of the cases the trunk was the site of predilection, and the head and neck were the next most frequent sites, being the sites in 23% of the cases. In this series, 70 patients were men and 22 were women, and the sex was not given in 11 cases. About 50% of these patients developed herpes zoster generalisatus.

Sporotrichosis. Presented by DR. J. F. SICKLEY.

Pustular Dermatitis Associated with Chronic Urinary Tract Infection and Contact Dermatitis. Presented by DRS. S. M. BLUEFARB and (by invitation) J. HASEGAWA and F. LEVIT.

Case for Diagnosis: Linear Scleroderma? Presented by DR. OTTO C. STEGMAIER, Davenport, Iowa.

Morphea. Presented by DR. OTTO C. STEGMAIER, Davenport, Iowa.

Chronic Dermatitis. Presented by DR. RICHARD Q. CROTTY, Omaha.

Pseudopelade and Seborrheic Dermatitis. Presented by DR. LOUIS G. SCHEIMANN (by invitation).

Xanthomas Tuberosum with Xanthic Tumors of the Tendon Sheaths. Presented by DRS. SAMUEL M. BLUEFARB, SILAS WALLK, and (by invitation) MARTIN L. GECHT.

Prurigo Gestationis; Family History of Atopic Eczema. Presented by DRS. THEODORE CORNBLEET, SIDNEY BARSKY, and (by invitation) HASSAN M. YAZDI.

Dermatitis Vegetans. Presented by DRS. DAVID V. OMENS and (by invitation) HAROLD D. OMENS and J. LATONI.

CHICAGO DERMATOLOGICAL SOCIETY

Nov. 20, 1957

Benign Hemangioendothelioma. Presented by Dr. David Omens and (by invitation) Drs. Harold D. Omens and Hassan M. Yazdi.

This 4-month-old girl had a dark-blue elevated firm nodule about 2 cm. in diameter adjacent to the right nipple at birth. Two months ago the lesion began to spread rapidly, appearing on the right shoulder, upper back, and arm. One month later she developed a dark-bluish, slightly elevated nodule on the calf of the leg.

Biopsy specimen is presented.

Verrucous Nevus. Presented by Dr. David Omens and (by invitation) Drs. Harold D. Omens and J. Latoni.

A 6-week-old Negro boy was born with these lesions.

The patient presents a disseminated monomorphous dermatosis involving the scalp, face, and neck and consisting of verrucous lesions in patches and bands, brownish and the size of millet seed.

Hemangioma. Presented by Drs. S. M. Bluefarb, Silas Wallk, and (by invitation) Hassan Yazdi.

This 57-year-old Negro woman states that three months ago she developed a small red painful pea-size nodule on the right index finger. A month ago she developed a macular lesion at the site of biopsy.

Biopsy specimen is presented.

Discussion on Preceding Three Cases

Dr. A. H. Slepyan: Dr. Bluefarb's case appears to be a granuloma pyogenicum or an infected angioma.

The first case shown at the Cook County Hospital with the lesion in the axilla is a rather unique one. The lesion felt indurated and ropy. This is not a true cavernous hemagioma but feels as if there were many vasoformative strands deep in the tissue. It is likely that there may be thrombosis deep in the area, giving this indurated feeling. I would suggest that a small dose of radiation be given to the area, since many of these lesions are highly radiosensitive. The lesion seen on the leg appears to be a cavernous hemangioma.

The second case belongs to the nevus hystrix group. The association with ocular changes and alopecia of the scalp would certainly make one think of an ectodermal defect occurring in this child.

Dr. F. J. Szymanski: The case of benign hemangioendothelioma is the most interesting and the most unusual case presented today. Clinically we see a tumor mass that resembles a cavernous hemangioma. Microscopically we see a very cellular vascular tumor that resembles a hemangioendothelioma. This type of tumor has been described by general pathologists, and despite the microscopic picture it is considered to be a benign tumor.

The names given to these vascular tumors have been infantile hemangioendothelioma and benign hypertrophic hemangioma. Despite the cellularity such tumors respond satisfactorily to radiation.

Thallotoxicosis. Presented by Drs. James R. Webster† and Stanley Huff and (by invitation) Dr. Martin L. Gecht.

This 4-year-old boy was admitted to the hospital on Oct. 10, 1957, with a history of tremors and ataxia for two days. He was listless; slurring of speech was noted. There was no history of medication or ingestion of chemicals. The patient had an upper respiratory infection with nausea and vomiting but no diarrhea one week prior to admission. However, his mother noted that his hair began to fall out about the same time.

The physical examination is essentially negative except that he exhibits purposeless movements when standing still and incoordination when doing simple things, such as shaking hands. The gait is definitely ataxic. Romberg's sign is positive. There is an intention tremor and nystagmus on extreme gaze.

During his hospital stay, he continued to lose hair, particularly over the parietal areas. There was some patchy erythema and scaling of the scalp. The Wood's lamp examination was questionably positive for fluorescence characteristic of Microsporum audouini infection of the scalp in some areas, but the KOH examination was negative. Cultures have not had time to grow.

A complete neurological study ruled out intracranial pathology, labyrinthitis, or cerebellar tumor.

X-ray examination of the skull and long bones did not reveal any abnormality.

On cardiac consultation no abnormalities were detected either clinically or in laboratory examinations, and so rheumatic fever was ruled out.

Laboratory findings: Urine: Specific gravity 1.022; albumin 2+; many white cells with pus clumps. Negative for arsenic. Subsequent urines were normal. Thallium 150 μg. per 100 cc. (Note: Qualitative study was markedly positive.) Blood: Hemoglobin 11 gm., 71%; red blood cells 4,400,000; white cells 4900, with 75% polymorphonuclear cells

Received for publication March 28, 1958.

† Dr. Webster died on Feb. 28, 1958.

and 22% lymphocytes. Rouleaux formation and atypical lymphocytes. Sickle-cell preparation negative. On Nov. 1, hemoglobin was 75% and white cell count was 7300. Sedimentation rate (corrected) 20 mm. in an hour. Spinal fluid examination normal except for decreased protein (12 mg. per 100 cc.; normal, 20-50 mg. per 100 cc.). Throat cultures: No pathogens grown. Electroencephalography normal. Serology normal. Blood studies for thallium: Qualitative studies, markedly positive; quantitative studies, 800 μg/100 cc. Studies for lead and arsenic were negative in the blood, urine, hair, and nails.

In the way of therapy patient was given Bal, 0.5 cc. b. i. d., and Artane, 2.5 mg. t. i. d.

Discussion

Dr. Marcus R. Caro: Many years ago I treated a number of children for ringworm of the scalp with thallium acetate. It was not a good treatment. All the hair fell out completely except for a peripheral frontal line. In this case the hair loss is not complete and this is not the usual picture of baldness due to thallium. If thallium were used in doses smaller than 8 mg. per kilogram body weight the hair would not fall out at all. This child must have ingested much more or the hair would not have fallen out at all, and, therefore, the hair loss should have been more complete if thallium were responsible.

Dr. Minnie O. Perlstein: I have been hearing about this child from my husband and son-in-law, both of whom are associated with the Pediatric Department of Cook County Hospital. The child was brought into the hospital with a neurologic problem and not as you saw him today. Today he is only restless; on admission, he was comatose and completely without hair except for a frontal fringe. The ataxia came on 24 hours prior to admission to the hospital. A diagnosis of poisoning by either arsenic or thallium was made. No history could be elicited for either substance. He was treated with Bal because metal poisoning was suspected. He got worse. He was given Artene. The Bal was stopped, but the Artene was continued. With Artene therapy the child made a most remarkable recovery. The mother denies any drug ingestion. We cannot find where the child got the thallium. We should make mention of the fact that Miss Berman, of the Illinois Masonic Hospital, is the one who made the thallium determinations. She said that there was a very high thallium determination.

Dr. Stephen Rothman: In the old days 1 to 11 mg. of thallium acetate per kilogram of body weight was given. Interestingly, in Europe many dermatologists still use one-half dose of x-ray and one-half dose of thallium for temporary epilation. This method is claimed to be effective.

Dr. Eugene Lorant: Some years ago when I was in training in dermatology we used one-half dose of thallium acetate and one-half dose of x-rays. We used thallium acetate, 3.5 to 4 mg. per kilogram of body weight, and one-half of the epilating dose of x-rays, and we had excellent results.

Dr. Michael H. Ebert: Years ago I also used thallium at Rush Medical College. We would get a good alopecia of the scalp hair, but the lanugo hair did not fall out.

Dr. Martin L. Gecht (by invitation): The alopecia started about the same time the clinical manifestations of central nervous system toxicity developed. This case was presented because there have been only 18 cases of thallium intoxication reported in American medical literature since 1935. Ten of these patients died. Alopecia is apparently an early finding, occurring about 10 to 15 days after the toxic blood level is reached. Association of alopecia with central nervous system disease manifestations, especially to those of us who have not used thallium in practice, should remind us of thallium or heavy-metal poisoning. There were 25 insect powders on the commercial market containing thallium in 1955. Fortunately, the incorporation of thallium into depilitory ointments has been prohibited by the Food and Drug Administration. There is still a considerable difference of opinion as to where thallium acts to cause the alopecia. The use of cystine has protected rats against alopecia. Recent work indicates that thallium disrupts the cellular differentiation which leads to keratin formation, possibly by interfering with utilization or incorporation of cystine into the keratin molecule. Thallium affects only hair in the growing phase. This child did not have total alopecia.

Hemochromatosis. Presented by Drs. Samuel M. Bluefarb, Silas Wallk, and (by invitation) Martin L. Gecht.

This 65-year-old white man was first admitted to Cook County Hospital during March, 1956, complaining of dyspnea. During this admission he presented hepatomegaly, splenomegaly, and an enlarged and erythematous tongue. Studies of blood chemistry at that time revealed severe liver damage. Ferrocyanide, 0.1 cc., was injected intradermally on the forearm. The skin became bluish-green immediately. A ferrocyanide test of the urinary sediment revealed bluish coloring of the epithelial cells. Cutaneous and liver biopsies were performed. These both confirmed the diagnosis of hemochromatosis.

Since this time the patient has had numerous phlebotomies. His present admission was because

of syncope, weakness, and melena. The etiology of the melena has not been established.

Laboratory findings (1956): Urine normal except for 2+ urobilinogen. Blood count: Hemoglobin 64%; white cells 9500, with 63% polymorphonuclear cells, 25% lymphocytes, and 8% monocytes. Serum iron 174 μg. %. Blood chemistry studies: Total protein 6.2 gm. per 100 cc. with albumin 2.1 gm. and globulin 4.1 gm.; cholesterol 91 mg. per 100 cc., esters 27% of total. Sulfobromophthalein 1.1%; cephalin flocculation 4+; thymol turbidity 7.8; γ-globulin turbidity 1.10. Fasting glucose 127 mg. per 100 cc.; two-hour glucose 255 mg. The glucose-tolerance curve today (Nov. 20, 1957) is normal.

Biopsy specimen is presented.

Discussion

DR. STURE A. M. JOHNSON, Madison, Wis.: Chelation therapy was found to be of some value by McMahon (*J. Lab. & Clin. Med.* 48:589 [Oct.] 1956).

DR. THEODORE CORNBLEET: The British have used phlebotomy to produce a negative iron balance. The ingestion of the metal, too, is reduced. In this way the iron stores and deposits in the tissues are tapped and reduced. The clinical results are said to be encouraging in this serious disorder. The patient needs reasonably close watching so that the induced iron and hemoglobin imbalance does not get out of hand.

DR. JULIUS E. GINSBERG: I thought that the picture resembled pellagra rather than hemochromatosis. The patient had dermatitis on the backs of the hands with postinflammatory hyperpigmentation. There was hyperpigmentation of the face. He had the pale color of many middle-aged persons. He had hemosiderosis in addition to what looked like pellagra.

DR. SAMUEL M. BLUEFARB: This patient has true hemochromatosis as demonstrated by histologic study of tissue from the liver removed by biopsy. The pigmentation which occurs in hemochromatosis may simulate that of Addison's disease, pellagra, or any one of several pigmentary diseases. This patient also has cirrhosis of the liver, evidenced by the sparse growth of hair on the scalp and chest, beginning atrophy of the testicles, and glossitis.

Fixed Drug Eruption (Sulfonamides). Presented by DRS. THEODORE CORNBLEET, SIDNEY BARSKY and (by invitation) MARTIN L. GECHT.

This patient had her first episode of an eruption consisting of erythema and bullae, with resulting hyperpigmentation, four years ago, at 3 years of age. During February, 1956, she had a similar eruption, with some new areas of involvement. The lesions were erythematous and bullous, with irregular shapes. She was presented to this Society at that time as a case of penicillin sensitivity, in accordance with the mother's story that she had received penicillin on both occasions for a pharyngitis. For the latter infection she had received a combination of penicillin and sulfonamides (sulfadiazine, sulfamerazine, and sulfamethazine). In August, 1957, she returned with a similar eruption after taking sulfisoxazole (Gantrisin). After recovering from this episode, she was patch-tested with Gantrisin in aqueous and ointment forms. No new lesions of a similar nature developed, although she did have a generalized eruption similar to miliaria crystallina in 48 hours.

We have now applied patch tests with Gantrisin in an ointment (ophthalmic) form on several areas near, upon, and away from the healed lesions.

Discussion

DR. ALBERT H. SLEPYAN: I believe that this is a very fine example of a fixed drug eruption. During World War II, at Great Lakes, we had 100,000 men who were given two pills of sulfadiazine each and every day as an experiment to keep them from developing sore throat and the streptococcic complications. Drug eruptions due to sulfadiazine were common and included fixed eruptions. One patient had come from another station with a history of a fixed eruption associated with a high fever and marked constitutional reaction. When he arrived at our base he was promptly given two pills which put this man back into the hospital with a fixed eruption involving the same areas and again with exceedingly high fever. It has been our experience that the sulfadiazine group is capable of producing fixed eruptions.

DR. THEODORE CORNBLEET: We had a twofold purpose in presenting this patient. It was to show a fixed drug eruption from Gantrisin, which I understand has not been reported before. In addition, patch tests with the drug put on or in contiguity with previous lesions were positive, whereas a patch at a distance was negative. We attempted to show this today, but unfortunately the dressings fell off.

Psoriasis. Presented by DR. S. J. ZAKON and (by invitation) DRS. C. PALMGREN and F. LEVIT.

This 2½-year-old boy was first noted to have skin disease shortly after his birth when he developed a rash in the diaper area. The mother states that this rash then spread to the rest of the body and has persisted through many remissions and exacerbations.

There is no history of psoriasis in the patient's family. A cousin of the patient's mother had eczema as a child, and the patient's mother had eczema of the body creases as a child.

The patient's health except for his skin disease is good. He has had several episodes of diarrhea since infancy but not to any unusual degree.

He has been receiving Diodoquin, 0.3 gm. t. i. d., since Nov. 1, 1957, with no apparent change.

Psoriasis of Five Months' Duration in a 1-Year-Old Boy. Presented by DR. I. M. FELSHER and (by invitation) DRS. C. PALMGREN and F. LEVIT.

Discussion on Preceding Two Cases

DR. CLARK W. FINNERUD: The first case presents psoriasiform lesions which I believe to be those of that type of pityriasis rubra pilaris. Such lesions can closely simulate true psoriasis, both clinically and histologically. The cases of the two children are remarkable because of the early age of onset of lesions, which clinically appear to be psoriasis. They deserve watching, however, in that such psoriasiform eruptions may prove to eventuate in something else.

Chronic Discoid Lupus Erythematosus Occurring in Three of Five Members of One Family. Presented by DR. A. M. BUCHHOLZ.

A married woman aged 33 has been under treatment for chronic discoid lupus erythematosus since 1949. When first seen, she had extensive facial lesions, which formed grotesque circumorbital and circumoral rings, and involvement of the scalp. There has been a gratifying response to the antimalarials and local application of carbon dioxide.

A man aged 35, the above patient's brother, developed chronic discoid lupus erythematosus at the age of 30. His major involvement is on his neck, and he is under active treatment of a dermatologist in his home town.

A man aged 40, the eldest brother, has lesions of face and neck, with principal involvement of the forehead. He is under treatment at present.

There are two other brothers, one of whom had "sores" of scalp, but we were unable to examine him. The fourth brother is free of any cutaneous eruption.

Discussion

DR. MICHAEL H. EBERT: I think that this is an interesting situation. There are three members of a family of five with chronic discoid lupus erythematosus. I have had at one time or another the good fortune to see and at times to treat a family of three women. One of these had acute disseminated lupus erythematosus and died in Presbyterian Hospital, where the postmortem examination confirmed the diagnosis. The other two have what one might classify as disseminated discoid, the type of discoid that is extensive on the upper back and extensors of the arms and much more marked than the ordinary discoid lupus erythematous but with very few systemic manifestations. These women, in their forties and fifties, are still living. They are the only members of the family. That does not mean that there is a genetic background for lupus erythematosus. One might expect that in a country of 150,000,000 there would be a few families where three in the family had lupus erythematosus.

DR. H. M. SHAIR, Quincy, Ill.: I have seen (1950-1952) three adult brothers with discoid lupus erythematosus. One developed a mild acute disseminated flare-up. I sent the biopsy material to Dr. Hermann Pinkus, who wrote: "I wonder if the changes here might possibly indicate some congenital weakness and might explain the familial incidence—the German Handbuch lists about 10 instances, one published by Michelson." I saw twin sisters with discoid lupus erythematosus at a St. Louis Dermatological Society meeting.

DR. SILAS WALLK: Familial cases of acute lupus erythematosus have also been reported in the literature.

DR. STURE A. M. JOHNSON, Madison, Wis.: Isoniazid, 50 mg. three times a day, with 250 mg. of chloroquine once a day has been of great value in the treatment of some of our patients with lupus erythematosus.

DR. ALEXANDER BUCHHOLZ: Touraine reported 49 families in which chronic discoid lupus erythematosus occurred in more than one member. In going over his entire series I find that he states that acute disseminated lupus erythematosus does not occur in families. Apparently this is not the finding from the members here.

Case for Diagnosis and Therapeutic Suggestions: Sarcoidosis? Presented by DR. SYLVIA F. GRIEM (by invitation) and DR. FRANK J. KENDRICK.

A 26-year-old Negro married woman, Mississippi born, was found to have extensive pulmonary changes on a mobile-unit microfilm in the summer of 1956. She was hospitalized in a tuberculosis sanitarium from Sept. 13, 1956, until Jan. 21, 1957, and treated with injections and pills. She was asymptomatic at the time, although her admission chest x-ray showed cloudy opacities in the upper lung fields and enlarged hilar glands. The admission diagnosis of moderately advanced pulmonary tuberculosis was changed to that of "probable sarcoidosis" after six gastric cultures were found to be negative for acid-fast bacilli and chest x-rays remained stationary. The blood cell count is said to have been normal, although the sedimentation rate was 80 mm. in an hour.

One month after admission to the sanitarium a symptomatic erythematous papule appeared on the nose which enlarged and persisted. A nodular hyperpigmented granuloma appeared below the

right knee a short time later. About six weeks ago many new papular and granulomatous lesions began to appear in the nostrils, at the mouth corner, in the corners of the eyes, and on the cheeks, elbows, and knees. The papules are erythematous and shiny. The more granulomatous lesions are scaly, and those over the elbows and knees tend to be hyperpigmented and verrucous.

She has shotty axillary and inguinal nodes but no hepatomegaly or splenomegaly.

Mazzini test was negative. No fungus was found on direct examination of the tissue. Cultures are not yet reported. Two biopsy specimens from the lesions on the right elbow are presented.

Pathological report: Sections of the nodule (No. 1082-57) show a chronic inflammatory infiltrate in the corium, closely applied to the epidermis, which shows reactive hyperplasia and hyperkeratosis. Sections of the smaller lesion (No. 1073-57) show granulomatous inflammation. In most of the granulomas there are Langhans giant cells.

PAS, acid-fast, and spirochete stains are negative.

Discussion

DR. STURE A. M. JOHNSON, Madison, Wis.: We have been treating a patient with intravenously administered edathamil disodium who has sarcoid disease involving the skin and lungs and concomitant malaise and pitting edema of the legs. The clinical improvement except for the cutaneous lesions has been dramatic. The clearing of the hilar and lung shadows, according to the x-ray department, has been unusual and impressive. I would suggest its investigation in this and other patients with sarcoid disease.

DR. BERNARD YAFFE: I wonder if calciferol was tried, and if not I suggest that it would be well to try it.

DR. ZACHARY FELSHER: I know of some experiments where the blood calcium was lowered in subjects by massaging edathamil ointment into the skin. I wonder whether the calcium levels were lowered in any of these people.

DR. STURE A. M. JOHNSON: In a fairly large series of patients treated with chelating compounds we have seen no dramatic lowering of the blood calcium. Originally we made blood calcium determinations daily and now do this once a week. Tetany, irritability, or other clinical evidence of calcium disturbance has not been seen by us.

DR. ADOLPH ROSTENBERG JR.: In the older literature there is much talk about the conversion of sarcoidosis into pulmonary tuberculosis. This is no longer seen at all frequently, for the prime reason that the x-ray diagnosis of sarcoidosis is not mistaken for tuberculosis; hence, such persons who have sarcoidosis are not put into tuberculous sanatoria, where they have an excellent chance to acquire tuberculosis.

Pseudopelade with Nail Dystrophy. Presented by DR. RICHARD P. REINERTSON (by invitation).

An 11½-year-old white girl was first noted to have longitudinal "cracks" in the fingernails and toenails at the age of 7, without any observed skin or paronychial changes. According to the mother, the patient received several x-ray treatments and the nails fell out within a year; they never have regrown properly.

In 1955, at the age of 9 years, the patient was noted to have had loss of hair from discrete areas of the scalp, associated with mild scaling but with no inflammation or pustules.

Past history is noncontributory. There is no family history of a similar condition. Review of systems is noncontributory.

Physical examination: There are severe atrophic and dystrophic changes of all fingernails and both great toes. In many places the nail folds have disappeared and the sites of nail plates are covered with normally keratinized epithelium. All right small toenails are deformed, exaggeratedly curved, and separated from the base; there are amorphous keratotic subungual masses.

On the vertex of the scalp are scattered several 4 to 5 mm., oval to round, atrophic areas lacking follicles. The surface of these lesions is thin and slightly depressed. Surrounding hairs and follicles are normal in appearance. There is mild keratosis pilaris of the upper and lower extremities.

Laboratory findings: Blood cell count and urinalysis were within normal limits. Kahn reaction was negative. X-ray of fingers showed no abnormalities. KOH examination and cultures for fungi from finger- and toenail beds were negative. Permission for biopsy was refused.

Discussion

DR. IRENE NEUHAUSER: The lesions in the scalp appear to be atrophic. As I remember, the atrophy in pseudopelade appears in characteristic patches described as footprints in the snow.

DR. STURE A. M. JOHNSON, Madison, Wis.: Is there anything characteristic of the nail dystrophy associated with pseudopelade so that one could make such a diagnosis without scalp changes or before they appear?

DR. STEPHEN ROTHMAN: I am not sure that the pseudopelade and the nail atrophy are related. However, Ormsby and Montgomery mention this combination, and thus it is possibly not pure coincidence. No fungi were found in the scalp lesions.

DR. MICHAEL H. EBERT: Many years ago, when I was still a postgraduate student in dermatology

at Rush Medical College, I presented what I believed to be a typical case of pseudopelade to Dr. Ernest McEwen, who had charge of the clinic that day. He examined it and found a few scales. In these I found the organism of favus. A few weeks later I made the same diagnosis and was again proved wrong. Since then I always make a careful examination of such cases, particularly if there is any nail involvement.

DR. RICHARD P. REINERTSON (by invitation): Clinically, this patient's atrophic noninflammatory scalp lesions are characteristic of pseudopelade. There was no history of inflammation, adherent scale, or crusting which might suggest folliculitis decalvans or favus. Unfortunately, permission for biopsy was not granted.

I was able to find in the literature just one other case of pseudopelade associated with nail atrophy. This case was reported by Saalfeld at the International Congress in Berlin, 1904 (cited by Photinos in "La Pseudo-Pelade de Brocq," Paris, A. Maloine et fels, 1930, p. 282).

Multiple Idiopathic Hemorrhagic Sarcoma Treated with Urethan. Presented by DR. MILTON ROBIN and (by invitation) DR. ROLAND MEDANSKY.

This patient aged 67 was presented previously at the Chicago Dermatological Society and is now presented for the second time to show improvement with urethan therapy after potassium arsenite solution and x-ray therapy proved ineffective. His blood cell counts have always remained normal, and the last one, on Oct. 21, during urethan therapy, was as follows: hemoglobin 15.3 gm.; white cells 6900, with 59% neutrophils and 41% lymphocytes.

Discussion

DR. S. M. BLUEFARB: I believe that we are all in agreement concerning the diagnosis of Kaposi's sarcoma. The history of any disease must be considered in order to evaluate the effectiveness of a drug. It should be remembered that sclerosis of the blood vessels will result in healing of many of the lesions in Kaposi's sarcoma. Dr. Michelson reported unfavorable results with urethan therapy in several cases of Kaposi's sarcoma.

DR. ROLAND S. MEDANSKY (by invitation): Possibly the urethan treatment had nothing to do with the result. The recommendation concerning urethan therapy is that it should be given in doses of 3 to 5 gm. per day. This man received 0.3 to 0.6 gm. per day. It is hard to decide whether the improvement was from the drug or because of spontaneous involution.

Case for Diagnosis. Presented by DRS. FREDERICK J. SZYMANSKI and (by invitation) GEORGE FLEMING.

This 53-year-old Negro man gives a history of hoarseness of approximately one year's duration. During March, 1957, he developed granulomatous lesions of the right external naris and tip of the nose. A study at Barnes Hospital, St. Louis, during June, 1957, revealed the following data.

Serology negative. PPD, first strength, strongly positive; histoplasmin positive; blastomycin negative. Findings on biopsy of lesions of the nose and larynx revealed caseating type of granuloma. Stains for fungi negative. Chest x-ray showed hilar and mediastinal adenopathy. Sputum smears were negative for acid-fast bacilli. Albumin 4.1 gm. %, globulin 3.9 gm. %, alkaline phosphatase 7.1 Bodansky units; calcium and phosphorus normal.

Patient has been given therapy consisting of aminosalicylic acid, 3 grams q. i. d., and isoniazid, 100 mg. t. i. d.

When the patient was seen at this hospital granulomatous lesions of the right external naris were noted. On the tip of the nose above the granulomatous zone there are a few discrete shiny infiltrated papules covered by an intact skin. On laryngoscopy granulations were noted on both pyriform sinuses. The epiglottis was fibrous and also revealed numerous granulations. The cords showed normal movement but were thick, beefy, and edematous.

Chest x-ray, blood tests, urine, serology, and sputum smears for acid-fast bacilli did not reveal any abnormality.

Histopathological report: Biopsy of the right upper lip was performed, and sections were stained with hematoxylin and eosin, Schiff-McManus, and Ziehl-Neelsen stains. The epidermis is hyperplastic with a thick scaly crust covering it. In the upper two-thirds of the corium, connective tissue is replaced by a very dense granulomatous infiltrate. The infiltrate is composed of numerous tubercles and by Schiff-McManus technique did not reveal any fungi. Acid-fast bacilli could not be found in sections stained by the Ziehl-Neelsen technique.

The sections from the biopsy specimen of this patient were reviewed by the Department of Pathology of the University of Illinois, and the impression of the reviewers was that it is chronic granulomatous inflammation of skin of upper lip, probably tuberculosis.

Discussion

DR. STEPHEN ROTHMAN: The clinical picture is reminiscent of that of rhinoscleroma. Caseation necrosis is extremely rare in the skin. Among all forms of cutaneous tuberculosis, it was observed only in tuberculosis miliaris faciei.

DR. SAMUEL M. BLUEFARB: A considerable number of patients having this type of nodular lesions on the nose are seen at Cook County Hospital. Examination invariably discloses the condition to be sarcoidosis. It is possible that further histologic studies of the lesion on the nose of this patient will show the typical picture of sarcoidosis.

DR. CLARK W. FINNERUD: Years ago Fred Weidman sent me some sections of sarcoid which were atypical in that they were loaded with Langhans giant cells. The sections demonstrated today reminded me of them.

DR. FREDERICK J. SZYMANSKI: There is a good chance that the final diagnosis will be sarcoidosis. We had a similar case in a Negro female with granulomatous lesion on the nose with a nonspecific histologic picture. We were confused until a third biopsy revealed the typical findings of sarcoidosis.

Nevoxanthoendothelioma. Presented by DR. MALCOLM SPENCER, Danville, Ill., and MAJOR HENRY L. HINES, Chanute Air Force Base, Ill.

The patient is a 19-month-old white boy with history of formation of xanthrochromic tumefactions on the trunk, face, and extremities since birth. The most recent lesion is approximately six months old and is over the left scapula. When first examined in December, 1956, he had hepatosplenomegaly and mitral systolic murmur in addition to skin lesions. Several older lesions, on face and wrist, have undergone spontaneous resolution, leaving a thin soft cicatrix at the site.

Findings on biopsy were reported as juvenile xanthoma by the Armed Forces Institute of Pathology. Blood cholesterol 140 mg. %; cholesterol esters 93 mg. %; hematology normal; serology negative. Urine normal. Total lipids 185 mg. %; phospholipids, 0.0 mg. %.

Histopathological report: Gross examination: Specimen consists of two ellipses of skin, the larger measuring 1 cm. in greatest dimension and containing a subcutaneous deposit of yellow material.

Microscopic examination: Sections of the larger specimen, labeled "active lesion," show a stratified squamous epithelium of skin type overlying a collagenous connective tissue dermis in which are aggregated sheets of histiocytes with large foamy cytoplasm and small centrally placed or eccentrically located nuclei. Interspersed among the masses of lipid histiocytes are several so-called Touton giant cells composed of rosettes of fused lipid histiocytes with a rim of uniform nuclei enclosing lipid-filled syncytial cytoplasm. Wavy bundles of eosinophilic collagenous fibers are also intermingled among the masses of lipid histiocytes. There is a large focus of condensed fibrous tissue, the individual cell nuclei of which are in varying stages of degeneration. These masses of degenerating fibrocytes appear to be surrounding masses of collagenous wavy material. Several endothelial lined vascular channels are enclosed within this process. An occasional coiled apocrine sweat gland is seen surrounded by lipid histiocytes. There is a fair sprinkling of lymphocytes and eosinophilic leukocytes among the lipid histiocytes.

Sections of the smaller lesion, labeled "atrophic lesion," show a stratified squamous epithelium of skin type overlying a dermis, the immediate subepidermal zone of which is composed of condensed collagenous fibers, and deeper to this are foci of lipid histiocytes with pale foamy cytoplasm and small nuclei, which aggregations are for the most part surrounding apocrine sweat glands. Several large vacuolated spaces presumed to represent fat vacuoles are seen contiguous with the accumulations of lipid histiocytes.

Diagnosis: Juvenile xanthoma.

Nevoxanthoendotheliomata. Presented by DR. LOIS G. SCHEIMANN (by invitation).

A 5-month-old girl developed an asymptomatic small "pimple" on the right side of her face and two similar lesions on her back at 2 months of age. The lesions slowly increased in size. At 5 months of age, new lesions appeared near the previous ones on her back and on the right lower leg.

Past and family histories, physical examination, and laboratory findings were noncontributory. Ophthalmological examination revealed no eye changes.

On the right side of her face is a firm 1×1 cm. lesion raised about 2.5 mm., with smooth shiny erythematous top. On her back is a group of three similar lesions, ranging from 3 mm. to 8 mm. in diameter. On her right lower leg are three slightly yellowish 3 mm. lesions.

Biopsy section is presented.

Histopathological report: The epidermis has been lost. In the corium there is a highly cellular infiltration, particularly dense in the upper corium. In the lower corium the cells infiltrate between collagen bundles in granulomatous fashion, and tiny vacuoles can be seen in their cytoplasm. There are no Touton giant cells. Mast cells are few.

Discussion on Preceding Two Cases

DR. DAVID W. KERSTING, Milwaukee, Wis.: It was worth traveling many miles for this opportunity to see and compare these two beautifully presented children.

The white boy with the flat ochre-yellow lesion has a typical xanthoma, while the Negro child has a few dull brownish-red smooth nodules, which clinically we may suspect are nevoxanthoendothe-

lioma. When we came to the histopathology of these we found in the sections that the first lesion consists of a very rich pure collection of foamy and clear histiocytes, the typical xanthoma cell, while the nodules in the other child consist of a tumorous mass of histiocytic and fibrocytic cells of all shapes and sizes, some foamy and clear and many not. There are a large number of the Touton type of giant cell, some lymphocytic infiltrate, and some fibrosis. This is the nevoxanthoendothelioma or juvenile xanthoma reported by Dr. Senear and Dr. Caro 21 years ago (*Arch. Dermat. & Syph.* 34:195-206, 1936), and recently thoroughly studied in a large series of children by Helwig and Hackney (*Am. J. Path.* 30:625-626, 1954), under the name of juvenile xanthogranuloma. This clinicopathologic pattern of juvenile xanthogranuloma as demonstrated by them is extremely rarely (if ever) attended by any systemic reticuloendothelial disease, defect of lipid metabolism, or xanthomatosis. I believe that this condition, seen here today in the Negro child, is closely related to our histiocytoma-dermatofibroma-sclerosing hemangioma-xanthofibroma group of local dermal histiocytic reactive granulomas and that the course is benign in all respects. In fact, these often regress and disappear without therapy. The true xanthoma of the other child, however, I view with alarm. Statistics and clinical experience tell us that a dermal xanthoma at this age is usually attended by a congenital alteration of lipid metabolism or other form of xanthomatosis.

DR. FREDERICK MALKINSON: In relation to the localization of the lesions of nevoxanthoendothelioma, there are very few cases reported in the literature describing involvement of tissues or organs other than the skin. Where such changes occur it is usually the eye that is involved, as first pointed out by Harvey Blank. Two years ago Dr. Griem and I presented such a case before this Society. The patient was a year-old girl with skin lesions present for nine months and left-sided ocular changes considered typical of glaucoma present for six months. A peripheral iridectomy was done, and sections of the iris and conjunctiva removed at surgery showed the same histologic appearance as that of the skin nodules.

Where eye involvement occurs in nevoxanthoendothelioma, the anterior chamber is affected with the characteristic changes of hemorrhage; histiocytic infiltration of the iris, sclera, and conjunctiva, and greatly increased intraocular pressure. The changes in the eye, then, are far more serious in their import than the skin lesions, which ultimately regress. In our patient visual acuity has remained 2/300 in the affected eye.

Pityriasis Lichenoides et Varioliformis Acuta (with Unusual Histologic Changes). Presented by DRS. BRIAN POTTER (by invitation) and LYDIA C. MARSHAK.

Biopsies of lesions in different stages of development were performed and gave the following findings: All sections show perivascular infiltration of inflammatory cells, chiefly mononuclear cells, and extravasation of red blood cells; some show definite vasculitis with beginning thrombosis and edematous separation of the layers of the vessel walls and indistinct staining of them. The more advanced lesions show degeneration of the upper corium and epidermis and finally their replacement by a necrotic crust.

Massive polymorphous collection of inflammatory cells beneath the epidermis, ordinarily seen in this disease, is lacking.

Discussion

DR. FREDERICK J. SZYMANSKI: The presenters made the comment that this case was one with very unusual histologic changes. I should like to disagree. The microscopic findings are typical of Habermann's disease. A vasculitis characterized by numerous lymphocytes surrounding and invading the superficial blood vessels is the essential microscopic alteration in this condition. Pathologic evidence indicates that Habermann's disease is not a form of parapsoriasis. It seems to be more closely allied to allergic vasculitis.

DR. D. W. KERSTING, Milwaukee, Wis.: Has Dr. Rostenberg included this syndrome among those which are suspected Shwartzman's phenomena?

DR. ADOLPH ROSTENBERG JR.: I do not know that there is any basis for attributing these lesions to a Shwartzman phenomenon. Dr. Szymanski tells me that in this condition one sees vascular alterations which suggest it may be on an allergic basis. Acute or chronic pityriasis lichenoides et varioliformis is unrelated to the other conditions labeled as parapsoriasis, except historically. It is thought that acute and chronic pityriasis lichenoides are related to one another, but the fact that the pathology in the acute form is very different from that in the chronic form raises a doubt as to this.

Case for Diagnosis: Xanthoerythroderma Perstans? Presented by DRS. STEPHEN ROTHMAN and (by invitation) ROGER W. PEARSON.

A 51-year-old white man first noted asymptomatic small brown scaly patches on both calves in 1950. The eruption gradually spread to involve all extremities and the lower abdomen. Few, if any, lesions have subsided spontaneously or with the use of benzoic and salicylic acid ointment

(Whitfield's ointment), which was irregularly applied until 1956. There is no history of drug intake.

The patient has a long-standing thyroid adenoma, but thyroid function is normal.

Physical examination: General examination is not remarkable except for large hard enlargement of right thyroid. Over the legs, anterior thighs, ventral surface of arms and forearms, and lower abdomen there are sharply circumscribed, slight, erythematous, yellowish-brown, oval, band-shaped, and irregular patches of varying sizes. Many patches show fine scaling and wrinkling. Infiltration is absent.

Laboratory data: Kahn reaction negative. Blood: White cells 6700, with a normal differential count; hemoglobin 15.9 gm. Erythrocyte sedimentation rate 4 mm. in an hour. Urine normal. Basal metabolism rate —1%, protein-bound iodine 5.0 mg. per liter; cholesterol 180 mg. %. Large chest film showed calcified thyroid adenoma on the right.

Biopsy section is presented. It shows a fine occasional parakeratosis and a mild banal chronic inflammatory infiltrate in the upper corium. Some cells of the latter are passing with focally edematous areas of the epidermis. There is mild perivascular inflammation.

Discussion

DR. MARCUS R. CARO: Why the variation of the name of parapsoriasis in this case?

DR. STEPHEN ROTHMAN: I agree with Dr. Caro that synonyms should be avoided if possible and that xanthoerythroderma perstans of Crocker and parapsoriasis en plaque of Brocq are identical. I used Crocker's term because of the definite yellow color of this lesion, indicating the good reasons for that name.

Planing on a Shoestring. Presented by DR. BERNARD YAFFE.

Demonstration and cost of necessary equipment for dermabrasion are shown.

Dremel power tool	$9.95
Resistance apparatus	3.50
Hair dryer	12.50
Wire brush	5.00
Ethyl chloride	0.90
Total	$31.85

Morphea. Presented by DRS. JAMES R. WEBSTER, STANLEY HUFF, and (by invitation) JOSE R. LATONI.

Syringoma. Presented by DRS. THEODORE CORNBLEET, SIDNEY BARSKY, and (by invitation) JOSE R. LATONI.

Case for Diagnosis: Cheilitis with Granulomatous Infiltrate. Presented by DRS. SAMUEL M. BLUEFARB, SILAS WALLK, and (by invitation) MARTIN L. GECHT.

Dermatomyositis. Presented by DRS. THEODORE CORNBLEET, SIDNEY BARSKY, and (by invitation) MARTIN L. GECHT.

Dermatomyositis. Presented (by invitation) by DRS. RICHARD P. REINERTSON and WILLIAM GILLESPIE.

Lepromatous Leprosy. Presented by DRS. THEODORE CORNBLEET, SIDNEY BARSKY, and (by invitation) JOSE LATONI.

Depigmented Nevus. Presented by DRS. JAMES R. WEBSTER, STANLEY HUFF, and (by invitation) HASSAN YAZDI.

Lichen Nitidus. Presented by DR. DAVID V. OMENS and (by invitation) DRS. HAROLD D. OMENS and MARTIN L. GECHT.

Linear Nevus. Presented by DRS. JAMES R. WEBSTER, STANLEY HUFF, and (by invitation) HASSAN M. YAZDI.

Case for Diagnosis: Psoriasis; Pityriasis Rubra Pilaris in an 8-Year-Old Girl? Presented by DR. FREDERICK J. SZYMANSKI and (by invitation) DRS. STEFAN BIELINSKI and ROLAND S. MEDANSKY.

Verrucous Linear Nevus Plus Secondary Infection of Left Knee (Parakeratosis Mibelli). Presented by DRS. IRENE NEUHAUSER and (by invitation) ROLAND S. MEDANSKY.

Deodorant Granuloma. Presented by DRS. SILAS WALLK and SAMUEL M. BLUEFARB.

Primary Localized Cutaneous Amyloidosis (Mucous Membranes Normal). Presented by DRS. ALFRED FALK and (by invitation) ROLAND S. MEDANSKY.

Contact Dermatitis to Thermo-Fax Paper. Presented by DR. SAMUEL M. BLUEFARB and (by invitation) DRS. J. HASEGAWA and F. LEVIT.

Contact Dermatitis to Thermo-Fax Paper. Presented by DR. SAMUEL M. BLUEFARB and (by invitation) DRS. J. HASEGAWA and F. LEVIT.

Case for Diagnosis: Erythema Multiforme Bullosa? Presented by DRS. ALFRED B. FALK and (by invitation) ROLAND S. MEDANSKY.

Case for Diagnosis: Drug Eruption? Presented (by invitation) by DRS. BRIAN POTTER and WILLIAM GILLESPIE.

CLEVELAND DERMATOLOGICAL SOCIETY

George M. Stroud, M.D., President
John A. Kenney Jr., M.D., Secretary
Robert Gardner, M.D., Reporter

Akron General Hospital

Nov. 21, 1957

Macular Atrophy (Anetoderma of Jadassohn). Presented by DR. HARLEY A. HAYNES JR.

A 33-year-old white woman for the past 10 years had slowly developed an increasing number of skin lesions, completely asymptomatic, over her arms, shoulders, and thighs. There was no history of any preceding chronic illness or skin disease.

There was a questionable history of von Recklinghausen's disease in an aunt.

Received for publication Feb. 28, 1958.

Examination of the skin reveals about 100 scattered lesions, appearing as slightly atrophic areas from 5 to 15 mm. in diameter, which apparently bulge slightly outward, with a wrinkled surface, although when palpated the lesions are definitely atrophic and give the impression of a depression. There is no change in color from the normal skin, nor is there urtication with friction.

A biopsy specimen was taken from a lesion on the left upper chest, and when a section of the skin was excised it not only seemed grossly atrophic but there seemed to be almost a vacuity under the skin, with absence of superficial fat. Histologic examination showed slight perivascular round-cell infiltration in the corium, fragmentation, and reduction in size and number of elastic fibers.

Discussion

DR. RUTH RAUSCHKOLB: In December, 1952, Dr. Earl Netherton studied and diagnosed a case of primary macular atrophy, Schwenninger-Buzzi disease. He presented it to the Cleveland Dermatological Society the following February, side by side with a case of secondary macular atrophy presented by Dr. John Rauschkolb. Dr. Netherton's patient was a woman in her forties, of Italian stock. No history of antecedent dermatosis could be obtained with this patient. Dr. Rauschkolb's patient was a woman in her seventies, of English stock. He had watched the atrophy evolve from a macular syphiloderm. At the time the patients were presented with their macular atrophy, no difference could be seen between the two.

In 1931 Chargin and Silver had presented an excellent paper on the subject of macular atrophy in the *Archives of Dermatology and Syphilology*. I reviewed the literature from 1931 to 1953, collecting reported cases of what has been considered a rather esoteric disease. Apparently the condition is not so rare. Many cases are seen and are not reported. This case is of real interest because it is possible to follow the evolution of the lesions in various stages. I should prefer to call it a primary atropy, multiple skin-like tumors of Schwenninger and Buzzi, because I could get no history whatever of any preceding dermatosis or of the erythema, which seems to be a diagnostic feature of the Jadassohn type. This young woman says the first lesion she noted was on her right elbow and occurred about the time of her marriage, in 1945. She has had others develop since and thinks that they may have some relation to pregnancy.

In later years Dr. Chargin has revised his opinion and feels that there is no primary macular atrophy and that all the cases are secondary to some preceding dermatosis, even though it may have been relatively inconspicuous. I have remained of the opinion that there is such a thing as primary macular atrophy insofar as there are cases in which you can establish no antecedent dermatosis. Certainly the essential feature is the disturbance in the elastic tissue, and I was very glad that there was a biopsy specimen in this case to show it. I know of no treatment for these conditions. The most recent literature on the subject comes from South America. There have been some excellent articles from Argentina and Brazil.

Granuloma Annulare. Presented by DR. WILLIAM C. MARSH.

Discoid Lupus Erythematosus. Presented by DR. A. L. LEIBY.

Case for Diagnosis: Epidermal Nevus? Presented by DR. WILLIAM DORNER JR. (by invitation).

Keratoderma Punctata. Presented by DR. FRANK M. MCDONALD.

Case for Diagnosis: Scarring Alopecia; Pseudopelade; Alopecia Areata; Lupus Erythematosus? Presented by DR. WILLIAM C. MARSH.

Urticaria Pigmentosa. Presented by DR. A. L. LEIBY.

Benign Pemphigoid. Presented by DR. HARLEY A. HAYNES JR.

Multiple Hazards of the Rubber Industry to Dermatology. Presented by MR. WILLIAM E. MCCORMICK, Director, Department of Industrial Hygiene and Toxicology, The B. F. Goodrich Company, Akron, Ohio.

Books

Medical Radiation Biology. By Friedrich P. Ellinger, M.D. Price, $20.00. Pp. 945. Charles C Thomas, Publisher, 301-327 E. Lawrence Ave., Springfield, Ill., 1957.

This authoritative volume should serve essentially as an excellent source of reference for all those concerned with radiation and its effects. The author, undertaking an ambitious project, has systematically recorded the available information in a concise logical presentation. In the first part of the book, the fundamental principles or radiation biology are set forth. The remainder of the book is then subdivided into discussions of the biology of ionizing radiation, utlraviolet radiation, and visible and infrared radiation, with emphasis on medical significance.

Throughout, the author is careful to point out which information is well documented and which is purely theoretical and also which is derived from animal study as distinct from human studies. There is a complete table of contents, which facilitates reference and helps somewhat to make up for the lack of an index. One-fourth of the book is devoted to a comprehensive bibliography of more than 5000 references.

The graduate student and the practitioner of dermatology, rather than the novitiate, will benefit most from this book, and for them it merits high recommendation.

Radium Isodoses—Radium Dosages in r-Units. By August Verhagen. Price, $4.65. Pp. 96, with 34 illustrations. Georg Thieme Verlag, Herdweg 63, (14a) Stuttgart N, Germany, 1958.

The traditional method of starting therapeutic radium dosages in "mgeh" (milligram element per hour) lacks accuracy in its clinical application. Especially in the therapy of cancer with massive doses, it is of utmost importance to have some knowledge of the amount of radiation which will reach the anatomical structures surrounding the lesion and to anticipate the intensity of reaction in that area.

By means of a special r-meter ("Gammameter," built by the Siemens-Reiniger-Werke, Germany), the author measured the r/hr. depth doses of certain quantities of radium, mounted in differently shaped applicators. He then recorded the measurements on graph paper and charted the isodose curves.

An introduction and brief explanations in German and English accompany the charts. Since the booklet is written by a gynecologist for gynecologists, it is of only limited practical value to the dermatologist.

ANNOUNCEMENT

Third International Congress of Allergology.—The Congress will be held in Paris, Oct. 19-26, 1958, sponsored by the International Association of Allergology and the French Allergy Association. As of June 1, six hundred seventy-five doctors have registered.

Program: (*a*) Symposia on asthma and emphysema, immunology, recent clinical advances, biochemical aspects, autoimmune reactions, dermatology, and socioeconomic aspects. Participants are world authorities in special fields—Pasteur Vallery-Radot, Löffler, Grabar, Dixon, Chase, Forsham, Sir Henry Dale, Halpern, Schild, Harrington, Dausset, Sulzberger, Jadassohn, and many others. (*b*) Sectional papers, limited to 10 minutes, on any phase of allergy. (*c*) Round-table small-group luncheon conferences on selected subjects led by international authorities. (*d*) Postconvention tours. (*e*) Social—a very enjoyable program has been arranged.

For registration and Congress information write to Dr. B. N. Halpern, 197 Boulevard St. Germain, Paris VII, France. For travel and postconvention tours write Thos. Cook and Son, 166 N. Michigan Blvd., Chicago.

throughout the practice of medicine . . .

anxiety

either alone or complicating physical illness

General Practice
Pediatric Psychiatry
Metabolic Disorders
The Neuroses
Neurology
Neuromuscular Disorders
General Surgery
Gastroenterology
Ob. & Gyn.
Cardiology
Dermatology
Allergy

Equanil®

Wyeth
Philadelphia 1, Pa.

Meprobamate, Wyeth

relieves tension–mental and muscular

localized
Ultraviolet
radiation

for

dermatology

Birtcher

spot-quartz

ULTRAVIOLET SPOTLIGHT

PROVEN EFFICACY IN A WIDE RANGE OF APPLICATIONS

A valuable adjuvant in the treatment of Acne, Eczema, Impetigo, Herpes Zoster, Erysipelas and other skin diseases, as well as infections and wounds. Produces desirable erythema with minimum pigmentation, allowing for better consistency in successive treatments. With the Woods' filter, a valuable diagnostic tool.

- *Produces first degree erythema at contact in 6 seconds. Ideal for administering to localized areas in any desired degree.*
- *Lightweight, weighs less than 3 pounds, no additional transformers or equipment. As easy to use as a flashlight.*
- *Ultraviolet emission in the germicidal band of 2540 Angstroms.*

MEDICAL JOURNAL REPRINTS AND DESCRIPTIVES ON REQUEST

THE BIRTCHER CORPORATION
Dept. AD-858
4371 VALLEY BOULEVARD
LOS ANGELES 32, CALIFORNIA

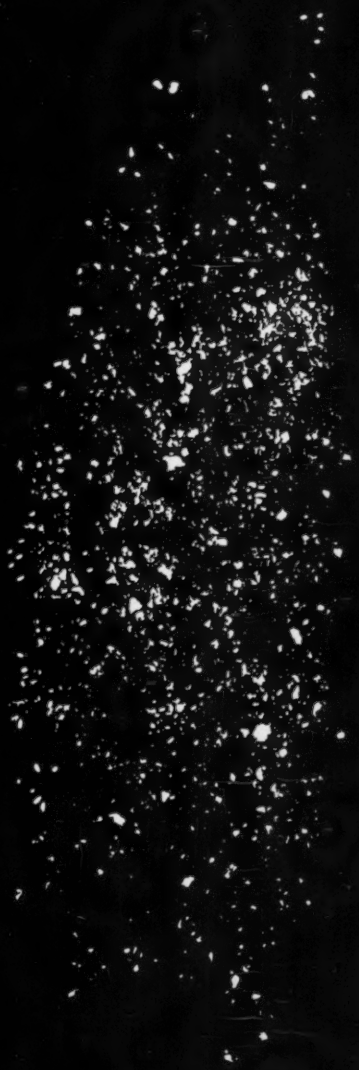
Please send me the Medical Journal reprints on Ultraviolet Therapy and descriptives of the BIRTCHER Spot-Quartz Lamp.

Dr. _____

Address _____

City _____ Zone _____ State _____

an advance in the treatment of seborrheic dermatitis



BEFORE

Capsebon

AFTER

Capsebon

introducing a new
cosmetic, therapeutic shampoo

Capsebon™

1% CADMIUM SULFIDE SUSPENSION

effective dandruff treatment
your patients
won't complain about

Capsebon

1% CADMIUM SULFIDE SUSPENSION

effective	...even in many patients who do not respond to other medication
well tolerated	Virtually nontoxic and nonirritating to eyes and skin...no special precautions
no rebound oiliness or dryness	...leaves hair soft and manageable
cosmetic elegance	Golden, creamy texture and light fragrance... no after-odor...abundant lather

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC.
INDIANAPOLIS 6, INDIANA

references:

1. Kirby, W. L.: Preliminary and short report. Cadmium sulfide suspension in seborrhea capitis. J. Invest. Dermat. 29:159 (Sept.) 1957. 2. Mullins, J. F., and Barnett, J. R.: Cadmium shampoo treatment of seborrheic dermatitis. Texas J. Med. 53:640 (Aug.) 1957. 3. Stough, D. B.; Lewis, R. A.; Farmer, B. L.; Osment, L. S., and Noojin, R. O.: New beneficial agents in the treatment of acne vulgaris and seborrheic dermatitis. To be published.

normal protective cover

Normal skin has an acid pH range between 4 and 6

Samples and literature on request

Supply:
ACID MANTLE Creme: 1 oz. tubes, 4 oz. & 16 oz. jars.
ACID MANTLE Lotion: 1 oz and 4 oz. squeeze bottles, 1 pint bottles.

ACID MANTLE®

CREME or LOTION pH 4.2

In housewives' eczema and industrial dermatitis, promptly restores and maintains the normal protective acidity of the skin. Active ingredient is aluminum acetate in specially formulated bases.

"The importance of a measure designed to return the pH of the skin quickly to its normal values after exposure to soap and alkalies is amply borne out..."

—Gross, P., et al.: A. M. A. Arch. Dermat. & Syph. 70:94,1954.

DOME *Chemicals Inc.*
109 WEST 64 ST., NEW YORK 23, N.Y.
665 N. Robertson Blvd., Los Angeles, Calif.
In Canada: 2765 Bates Rd., Montreal, P.Q.

Pleasingly and efficiently
serving patient and physician
during all seasons

SUPERFATTED

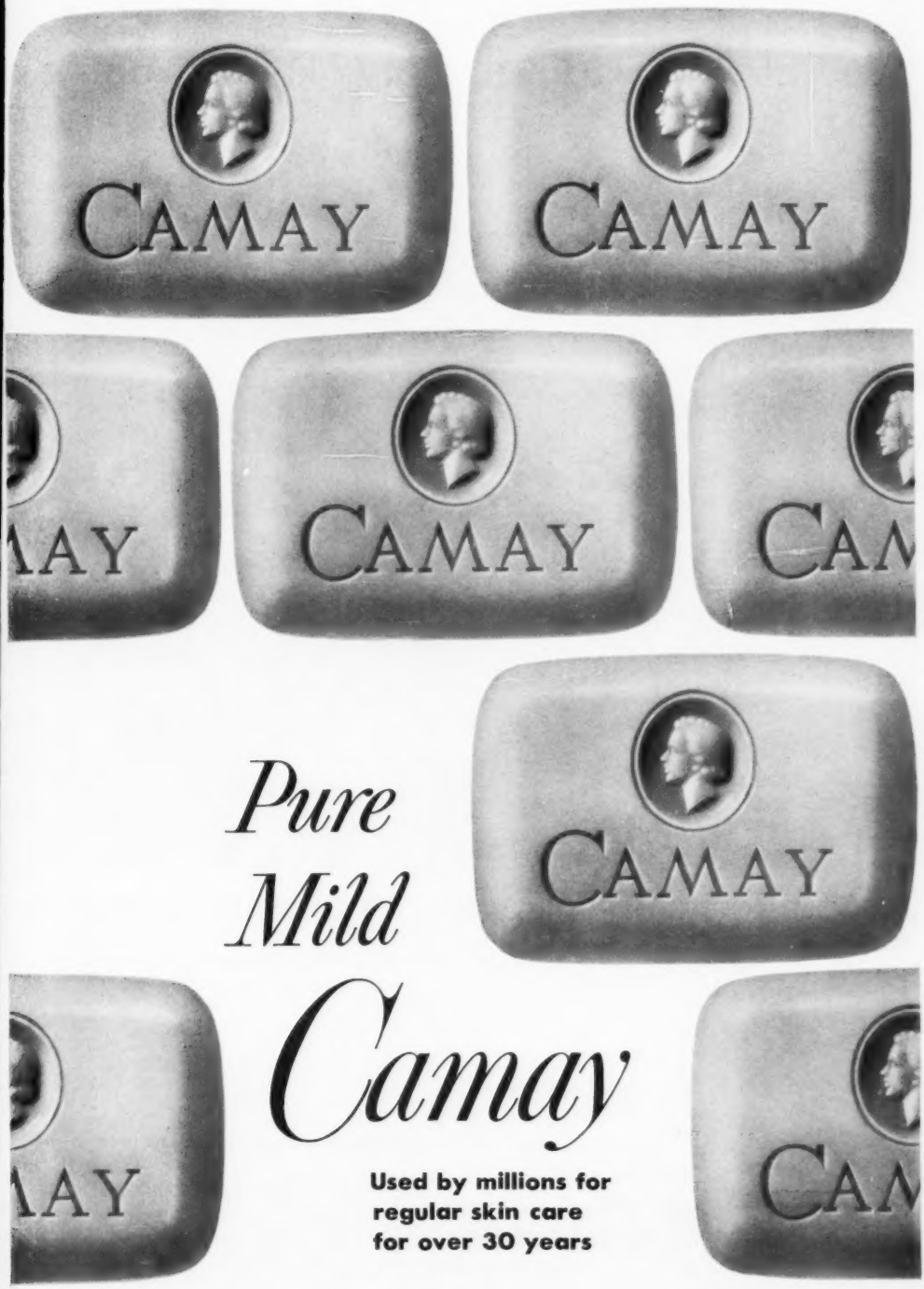
BASIS® SOAP

For dry sensitive skin

Available at Prescription Pharmacies

DUKE LABORATORIES, INC.
SOUTH NORWALK, CONN., U.S.A.

Mfrs. of Aquaphor®—Elastoplast®



Pure
Mild
Camay

Used by millions for regular skin care for over 30 years

©P&G Procter & Gamble

One of the beautiful things about women...

hypo-allergenic cosmetics by Beauty Counselor

Applied hygienically, in the home, by appointment, under a trained Counselor's guidance.

Physicians are invited to use this coupon:

Beauty Counselor®

CUSTOM-FITTED COSMETICS

GROSSE POINTE, MICH. • WINDSOR, ONTARIO • LONDON, ENGLAND

Beauty Counselors, Inc., Grosse Pointe 24, Michigan

☐ Please send me your qualitative formulas.

☐ Please arrange a home demonstration, without obligation, for my wife. D-88

*NAME*_____

*OFFICE ADDRESS*_____

*HOME ADDRESS*_____

*CITY*_____ *ZONE*_____ *STATE*_____

Incorporated in exclusive ACID MANTLE® vehicle

Quick Soothing Topical Response

IN INFLAMMATORY DERMATOSES

Cort-Dome™

Acid Mantle-Hydrocortisone

CREME AND LOTION—pH 4.6

ABATES INFLAMMATION AND RESTORES NORMAL SKIN ACIDITY

"Susceptibility to infection by bacteria is widely held to be due to the removal of the antibacterial 'acid mantle' of the skin and its displacement by an abnormal 'alkaline mantle'."—Fabricant, N. D.: A. M. A. Arch. Otolaryn. 65:11, 1957.

Supply—⅓%, 1% and 2% hydrocortisone in either Creme (½ oz., 1 oz., 2 oz., 4 oz. tubes and 1 lb. jars) or Lotion (½ oz., 1 oz., 2 oz., 4 oz. squeeze bottles and pt. bottles).

Samples and literature available on request.

Dome Chemicals Inc.

NEW YORK 23 • LOS ANGELES 46 • In Canada: 2765 Bates Road, Montreal

In Acne

TUCKS®

soft cotton flannel pads saturated with witch hazel (50%) and glycerine (10%). pH about 4.6

answers a dermatologic and an emotional need

Cleansing, solvent, mildly astringent TUCKS provides a new and valuable therapeutic aid for the treatment of acne.

At home in their handy jars, or *at school* in the moisture-tight plastic envelope provided, soothing Tucks pads promote the thorough skin care indispensable to the successful treatment of acne.

Always ready for use, TUCKS encourages cleanliness when used as finger shields for expressing comedones.

fuller PHARMACEUTICAL COMPANY
Minneapolis 16, Minn.

For a generous office supply of TUCKS —just fill in and return this card.

Name_____

Address_____

City_____ Zone____ State_____

AN *Ethix* FORMULA

UNSCENTED

SHAMPOO

Myristic and lauric acids saponified with polyamine alkali to a low pH(8), with neutralized polycarboxylic acid, enriched with lanolin esters, given extraordinary solvency with propylene glycol.

Vegetable or mineral tars may be added in desired percentage.

Removes ointments and medications gently but thoroughly.

High foaming, extremely economical in use.

Tolerated by scalps which shed epithelium from overstrong detergents.

RETAIL PRICE $1.50 BOTTLE 6 OZ.

ETHIX CORPORATION
P. O. Box 115, Inwood 96, L. I., N. Y.
Send 1 oz. sample bottles of ETHIX FORMULA Shampoo to:

.....M.D.

.....

.....

NEW non-inflammable Gebauer's FLURO-ETHYL

(FLUORINATED-HYDROCARBON)

FLURO-ETHYL is a solution of Ethyl-Chloride and Dichlorotetrafluoro-ethane which has been demonstrated to be useful as a topical refrigerant for use in plastic surgical skin planing and as an agent to produce local anesthesia for minor surgical procedures. It contains 75% Dichlorotetrafluoro-ethane and 25% Ethyl-Chloride, and when applied topically to the skin, produces rapid refrigeration and anesthesia to the desired depths of the skin.

CLINICAL USES:

Plastic Surgical Skin Planing: In the refrigeration dermabrasion technique GEBAUER'S FLURO-ETHYL is a refrigerant of choice because it eliminates the necessity of a blower. The mixture is non-inflammable and it produces rapid anesthesia and refrigeration to the required depths of the skin. In addition, the mixture does not give the patient a feeling of suffocation if inhaled. The area to be refrigerated can easily be controlled to the desired limits.

Although this preparation is specially designed for plastic surgical skin planing, it can also be used as a local anesthetic for minor procedures such as incision of furuncles, electrocautery to small cutaneous tags, flat warts, and nevi, or the alleviation of needle pain during hypodermic injection.

HOW IT'S USED

When using GEBAUER'S FLURO-ETHYL, holding same in an inverted position, the solution is then delivered onto the skin in the form of a fine, mist-like spray, producing a degree of anesthesia by refrigeration adequate for skin planing without the use of an air blower. To obtain best results place container in cooler before using.

MANUFACTURED BY

THE GEBAUER CHEMICAL CO.

CLEVELAND 4, OHIO

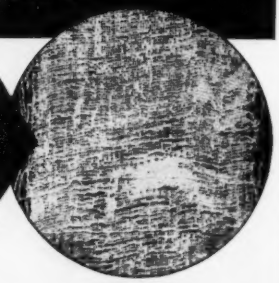
THE BEST IMPROVEMENT YET IN *UNNA'S BOOT*

NEW 4" x 10 YD.

Non-Ravelling

DOME-PASTE® BANDAGE

DOME

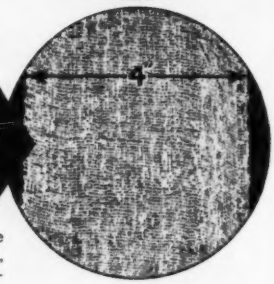


THE OLD

Frayed edges, uneven impregnation, difficult to apply.

•

Thread-locked edges, firmly woven; medicament spreads uniformly, easy to apply.



THE NEW

The new Dome-Paste bandage is flesh colored, 4" x 10 yd. gauze bandage... impregnated with glycerine, zinc oxide, gelatine paste.

RECOMMENDED

for leg ulcers resulting from thrombophlebitis (particularly the post partum and post-operative kinds), stasis edema and chronic venous insufficiency associated with varicose veins, and varicose eczema, lymphatic edema and thrombophlebitis of the superficial saphenous vessels.

AVAILABLE

Individually wrapped in sealed polyethylene bags, inserted in metal cans to insure freshness.

DOME
CHEMICALS INC.
109 WEST 64th ST. NEW YORK 23, N.Y.

A. M. A.
AMERICAN JOURNAL
OF
DISEASES OF
CHILDREN

integrate your knowledge—
subscribe to

A. M. A. Archives of PATHOLOGY

A. M. A. Archives of INTERNAL MEDICINE

A. M. A. Archives of OPHTHALMOLOGY

A. M. A. Archives of OTOLARYNGOLOGY

For a more complete reference shelf, we recommend these related journals. The variety of fields covered are especially appealing to the general practitioner with special interests. Each issue is important to your practice. Begin your subscriptions TODAY.

Department (D. C.)
AMERICAN MEDICAL ASSOCIATION
535 N. Dearborn St.
Chicago 10, Ill.

Begin my subscription(s) NOW, for:

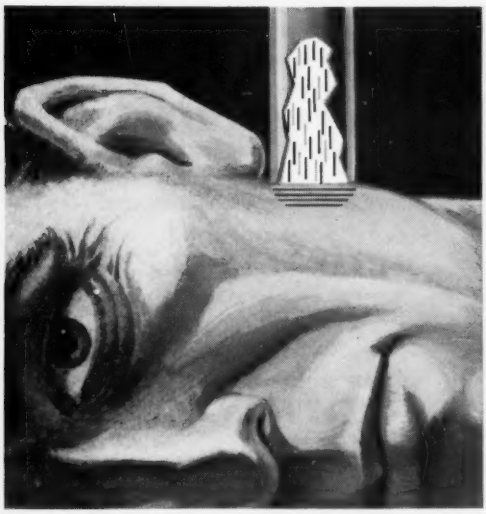
A. M. A. .....

NAME .....

STREET .....

CITY .....STATE .....

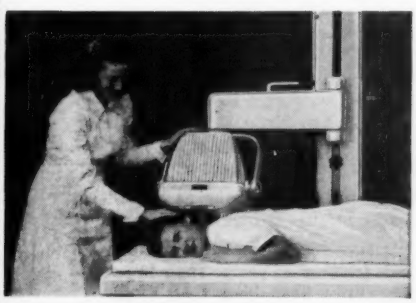
G-E Maximar® 100 for superficial therapy...



CONVENTIONAL UNITS. Glass, oil and bakelite absorb soft radiation (gray lines). Unit must operate at higher voltage, increasing amount of hard radiation (black) which causes penetration as deep as one cm.

MAXIMAR 100. Beryllium window minimizes absorption of soft rays. Radiation is concentrated in superficial layers of tissue with consequent reduction in percentage of dose received by the deeper tissues.

up to 84% absorption in first 4 mm of tissue



Quality of radiation—number one in a host of reasons the Maximar 100 is unsurpassed. Its versatile range extends to 100 kvp, under exact control all the way. Operates at high or low intensities with precise or broad field coverage — over an 18-cm circle at 30-cm focal-skin distance. And its maneuverability makes you the fast master of any technic.

Ask your General Electric x-ray representative for an introduction to the Maximar 100. Or you can get full data — features and specifications — by writing X-Ray Department, General Electric Company, Milwaukee 1, Wisconsin, for Pub. P-82.

OPERATION up turn GENERAL ELECTRIC

You'll never buy better than now

Progress Is Our Most Important Product

GENERAL ELECTRIC

The
1-2-3 Treatment
for
Warm Weather Dermatoses

Poison ivy, poison oak, insect bites, Anogenital eczema, athlete's foot, superficial mycoses, Acute and subacute contact and allergic dermatitis.

Samples and literature on request

1 ACUTE STAGE
DOMEBORO® pH 4.2
Cool Wet Dressings
DOME

2 POST TREATMENT
ACID MANTLE®
Creme pH 4.2 • Lotion pH 4.5
DOME

3 FOR DESTROYING FUNGI
QUATRASAL®
Fungicidal Spray
DOME

DOME Chemicals Inc.
NEW YORK 23 • LOS ANGELES 46 • In Canada: 2765 Bates Rd., Montreal

THE MOST TRUSTED NAME IN DERMATOLOGICALS

1. DOMEBORO (Burow's Solution)
2. ACID MANTLE (aluminum acetate in specially formulated bases)
3. QUATRASAL (salicylanilide, trimethyl octadecyl ammonium pentaclorophenate, and isopropl alcohol 94%)

AR-EX
hypo-allergenic
COSMETICS

A complete, clinically-tested system of beauty care

AR-EX Products are preferred by your patients for their cosmetic elegance.

A first choice of physicians as a safeguard against known cosmetic allergens.

AR-EX Cosmetics have been recommended by physicians for over 23 years. Their hypoallergenic qualities have been long established by repetitive testing on allergic patients. AR-EX COSMETICS are produced by the company's original founders, the only independently-owned producers of hypoallergenic cosmetics.

AR-EX Products are available to pharmacies through their drug wholesaler.

WRITE FOR FREE FORMULARY

AR-EX PRODUCTS CO., 1036 W. Van Buren St., Chicago 7, Illinois

The Cosmetic Answer

More and more doctors are coming to realize that the problems of many of their patients can be answered by the intelligent use of the right cosmetics.

Frequently, disfiguring marks can be effectively concealed with a resultant improvement in the subject's general outlook on life.

There are many periods in a woman's life when an interest in improving her appearance goes a long way towards restoring a sense of well-being.

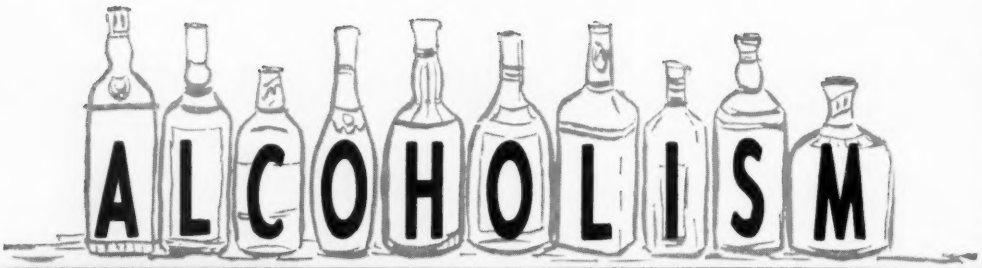
We suggest that a normally healthy person enjoys looking attractive as well as feeling fit.

We also suggest that the services of a Luzier Cosmetic Consultant can be of help in all cases where a restoration of self-confidence is a factor.

Luzier Inc., Makers of Fine Cosmetics & Perfumes

GIE

KANSAS CITY 41, MISSOURI



an important problem in today's living...

The following articles from TODAY'S HEALTH are now available in pamphlet form.

ALCOHOLISM IS A DISEASE. A discussion by the Chairman of the A.M.A. Committee on Alcoholism. by Marvin A. Block, M.D., 8 pages, 15 cents.

I AM THE WIDOW OF AN ALCOHOLIC. Three articles combined. by Virginia Conroy, 16 pages, 20 cents.

HOW EXPERTS MEASURE DRUNKENNESS. A partial transcript of an actual courtroom case. by H. A. Heise, 8 pages, 15 cents.

BARBITURATES, BOOZE AND OBITUARIES. A discussion of the dangers of mixing alcohol and barbiturates. by Donald A. Dukelow, 4 pages, 10 cents.

TWELVE STEPS FOR ALCOHOLICS. A frank discussion of the meaning of an alcoholic behavior. by Richard Lake, 6 pages, 10 cents.

These articles are available in one pamphlet for 50c

ALCOHOLICS ANONYMOUS. Written from the standpoint of a member, the basic treatment procedures are described and the psychological problems confronting the alcoholic are discussed.

ALCOHOL AND CIRRHOSIS OF THE LIVER. Relationship between alcohol, diet and cirrhosis. Increasing stress on nutritional differences. by Russell S. Boles.

HOW TO HELP A PROBLEM DRINKER. Understanding the alcoholic's capabilities, the necessity of help, causes of his condition. by Edward A. Strecker and Francis T. Chambers, Jr.

THE TREATMENT OF ALCOHOLISM. Tracing the steps from convincing the alcoholic that he is sick through treatment and cure. by Lewis Inman Sharp.

CONDITIONED REFLEX TREATMENT OF CHRONIC ALCOHOLISM. Its place among methods of treatment today, its development and correlation with personality factors. by Walter L. Voegtlin.

INSTITUTIONAL FACILITIES FOR THE TREATMENT OF ALCOHOLISM. Comparative differences, in drinking, with the last century, new establishments and methods of treatment, lack of trained personnel. by E. H. L. Corwin.

ADDRESS REQUESTS TO

ORDER DEPARTMENT
AMERICAN MEDICAL ASSOCIATION
535 N. DEARBORN ST., CHICAGO 10, ILLINOIS

UNEXCELLED PATIENT COMFORT and safety with DYCLONE™

dyclonine hydrochloride

an unsurpassed topical anesthetic

for
instrumentations
examinations
pain
pruritus

DYCLONE is a well tolerated topical anesthetic which is

fast-acting
long-acting
antibacterial
antifungal
virtually nonsensitizing

supply... Dyclone Creme, tubes of 1 oz. with rectal applicator. Dyclone Solution, bottles of 1 and 8 oz.

PITMAN-MOORE COMPANY
DIVISION OF ALLIED LABORATORIES, INC.
INDIANAPOLIS 6, INDIANA

OUTSTANDING ANHIDROTIC ANTICHOLINERGIC

"THE CLINICAL REPORTS[1] HAVE SO FAR BEEN FAVORABLE"

BANTHINE®

improves skin disorders associated with excessive perspiration—

By blocking the cholinergic innervation of the sweat glands, Banthine (brand of methantheline bromide) promptly reduces excessive perspiration. Observations by Perry and his associates[2] provide objective evidence of profound reduction of sweat gland activity following the administration of Banthine. Banthine is widely used as adjunctive therapy in skin disorders associated with hyperhidrosis.

Use of Banthine is described[1] in Wiener's recent text: "The main indication for dermatologic use is hyperhidrosis, but it has also been found useful in the control of normal sweating, in dyshidrotic vesicular eruptions, in intertrigo, in contact dermatitis, and in suppurative hydradenitis axillaris. The average initial adult dose is 50 mg. administered orally or parenterally. More or less may be given three times daily, but the daily total should not exceed 450 mg. The daily dosage in the treatment of hyperhidrosis is 100 to 200 mg., but higher doses may be necessary. . . . Following a dose of 100 mg., dryness of the palms usually sets in after thirty to forty-five minutes and lasts four to five hours. . . . The clinical reports have so far been favorable."

Banthine is also recommended[3] for the hyperhidrosis occurring with *Tinea pedis*.

1. Wiener, K.: Systemic Associations and Treatment of Skin Diseases, St. Louis, The C. V. Mosby Company, 1955, pp. 329; 458-459.
2. Perry, D. J.; Mount, G. D., and Browne, B. W.: The Effect of Varying Oral Dosages of Banthine, Pro-Banthine and Prantal on the Galvanic Skin Response, J. Invest. Dermat. 28:239 (March) 1957.
3. Olansky, S., and Callaway, J. L., in Modern Medicine 1958 Annual (Part 1): Management of Superficial Infections, Minneapolis, Modern Medicine, 1957, p. 46.

SEARLE *Research in the Service of Medicine*
G. D. SEARLE & CO., CHICAGO 80, ILLINOIS

"...soothing and nonirritating and especially helpful in allaying the itching."*

Prophyllin® wet dressings

PROPHYLLIN combines sodium propionate and water-soluble chlorophyll derivatives in a wet dressing of unusual effectiveness. Complete healing or significant improvement in over 100 patients with various dermatologic lesions led the reporting physicians* to state: "It (PROPHYLLIN) seems to be particularly useful because of its (a)...physiologic action; (b) lack of toxicity; (c) bacteriostatic and fungistatic properties, and (e) soothing, healing, and especially antipruritic effects."

particularly useful in acute contact dermatitis

In 40 cases, PROPHYLLIN was considered "...a wet dressing of choice, even where there was some secondary infection."*

PROPHYLLIN Powder, for preparation of wet dressings, in cartons of 12 packets. (Each packet contains 2.3 Gm. of powder, sufficient to prepare 8 ounces of solution containing 1 per cent sodium propionate and 0.0025 per cent water-soluble chlorophyll.) Also in 4-ounce and 16-ounce jars.

PROPHYLLIN Ointment, in 1½-ounce and 4-ounce tubes. (PROPHYLLIN Ointment contains 5 per cent sodium propionate and 0.0125 per cent water-soluble chlorophyll.) Provides the benefits of PROPHYLLIN for ambulatory patients and where a wet dressing is contraindicated or impracticable.

*Peck, S. M.; Traub, E. F., and Spoor, H. J.: A.M.A. Arch. Dermat. & Syph. *67*:263, 1953.

Rystan company Mount Vernon, N. Y.

27697

effective ... in the full range of SUMMER DERMATOSES

Poison Ivy · Sunburn · Prickly Heat · Insect Bites

Humidity Rash · Chafing

2 types of AVEENO® Colloid Baths

For calming effect

AVEENO®
Colloidal Oatmeal

time-tested
widely accepted

AVEENO® Colloidal Oatmeal is available in 18 oz. and 4 lb. boxes.

For calming . . .
plus extra emolliency

AVEENO®
"OILATED"

Active Ingredients: Colloidal oatmeal concentrate, liquid petrolatum and hypo-allergenic fraction of lanolin.

AVEENO® "OILATED" is available in 10 oz. cans.

AVEENO Corporation

Pioneers in Ethically-Promoted Colloid Baths

PRESCRIPTION

℞

despite the advent of steroids...

'Pragmatar' remains a basic medication

in many common skin disorders.

- in seborrheic affections (including "cradle cap" and dandruff)
- in subacute and chronic dermatitis
- in eczematous eruptions
- in fungous infections (including "athlete's foot")

Pragmatar* tar-sulfur-salicylic acid

effective, easy to use, possesses
a wide margin of safety

Smith Kline & French Laboratories, Philadelphia

*T.M. Reg. U.S. Pat. Off.

SEBASUM*

*TRADEMARK

SEBASUM is effective as an aid in treating Acne. A pleasantly scented solution containing polysorbate 80, U.S.P., alcohol and acetone, SEBASUM removes excess oils from the skin, penetrating the sebaceous follicles through the action of its emulsifying and cleansing agents. Widely used in treating Acne and other seborrheic conditions, SEBASUM prepares the skin for supplemental therapy, if indicated. SEBASUM is well tolerated. It is pleasant and comforting to the patient. SEBASUM evaporates readily and will not stain or leave greasy residuals.

SEBASUM is packaged in attractive four fluidounce and pint bottles.

Ask your pharmacist to stock SEBASUM for your prescriptions.

Additional literature and samples sent on request.

SUMMERS LABORATORIES
INCORPORATED
AMBLER, PENNSYLVANIA

Of interest to you

and your patients

THE MENACE OF ALLERGIES

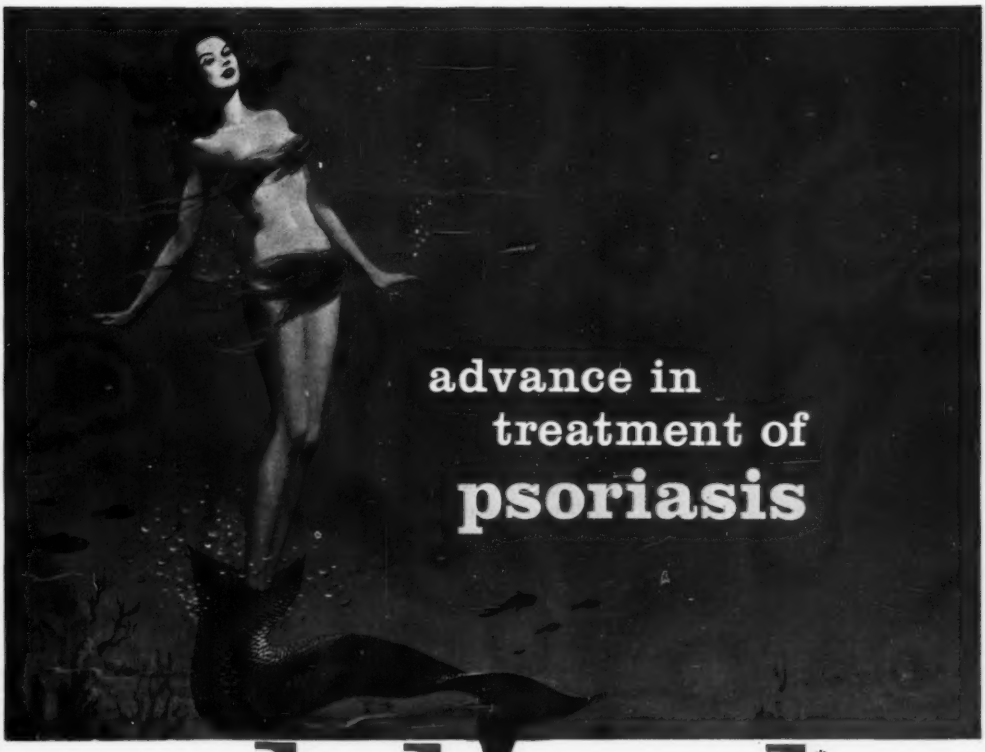
WHAT WE KNOW ABOUT ALLERGY
by Louis Tuft, 12 pages, 15 cents

FOOD ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

SKIN ALLERGY
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

ASTHMA AND HAY FEVER
by Samuel M. Feinberg, M.D., 6 pages, 10 cents

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET • CHICAGO 10 • ILLINOIS



alphosyl*

LOTION

Affords keratin-dispersing action[1]: Keratolytic, removes nonviable tissue, promotes healing.

Successful results ranging to complete clearing obtained[2-4] in patients with: • scalp-to-toe psoriasis • psoriasis of many years' duration • psoriasis involving tender areas.

Treatment-fastness rarely occurs: Recurrences (when treatment is discontinued) clear up again on resumption of therapy.

Well tolerated: Even when applied to lesions in anogenital and submammary regions.[2] Potential hazards of other therapies – mercury, arsenic, corticosteroids, x-rays – are avoided.

A noteworthy advance cosmetically: Nongreasy, nonstaining; vanishes on application to the skin. May be used freely on the scalp.

Application: Rub into lesions 2 to 4 times daily as indicated. Where heavy scaling or crusting occurs, the usual bath, to soften and facilitate removal of scale, is recommended before applying lotion.

Residual redness and pigmentation may remain up to several months but will eventually disappear. Once the condition is under control, daily to weekly application may prove satisfactory for maintenance.

In some cases, a seeming excessive scaling and drying may occur during therapy. This is an occasional phase of the healing process and usually precedes improvement. Patients should be advised of this and encouraged to continue therapy.

Formula: Allantoin 2% and special coal tar extract 5% in a lotion base.

Supplied: Bottles of 8 fl. oz.

(1) Flesch, P.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (2) Bleiberg, J., and Saltzman, J. A.: Clin. Med. *5*:485 (Apr.) 1958. (3) Bleiberg, J.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). (4) Clyman, S. G.: Reported Conf. N. Y. Academy Science May 9, 1958 (In Press). *Trademark

R&C **REED & CARNRICK** • Jersey City 6, New Jersey

QUARTERLY CUMULATIVE INDEX MEDICUS

YOUR GUIDE TO MEDICAL LITERATURE

Divided into sections, one devoted to books and the other to periodical literature, the QUARTERLY CUMULATIVE INDEX MEDICUS contains a list of current publications alphabetized as to authors and subjects. The exact bibliographic reference is given under the author with titles in the original language, while titles under subjects are all in English. The index also includes a listing of journals, addresses and publishers.

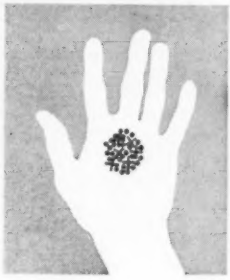
LISTED BY AUTHORS AND SUBJECTS

The QUARTERLY CUMULATIVE INDEX MEDICUS appears twice a year; volumes are cloth bound and cover periodicals for six months as indicated on the publication. These two volumes will be a convenient and inclusive reference for current medical literature. Invaluable for practitioners, specialists, teachers, editors, writers, investigators, students and libraries.

SUBSCRIPTION PRICE $25.00 PER YEAR
CANADIAN AND FOREIGN $27.00 PER YEAR

AMERICAN MEDICAL ASSOCIATION
535 NORTH DEARBORN STREET
CHICAGO 10, ILLINOIS

DERMATOSES



HERE ARE THE RESULTS WITH ORAL KENACORT:[1-5]

Number of patients		Daily maintenance dosage range (mg.)	Results: Excellent or good	Fair	Poor
Psoriasis	14	6-16	10	3	1
Nummular eczema	2	4-6	2		
Alopecia areata totalis	2	8, 32*	2		
Eczematoid dermatitis	2	8	2		
Atopic dermatitis	29	3-12	27	2	
Contact dermatitis	2	8	2		
Dermatitis herpetiformis	2	4-6	2		
Exfoliative dermatitis	3	10-12	3		
Giant urticaria	3	32*	3		
Pemphigus vulgaris	1		1		

**Initial suppressive dose, no maintenance dosage necessary.*

KENACORT IS A NEW, IMPROVED CORTICOSTEROID WHICH PRODUCES EXCELLENT CLINICAL RESPONSE

- *low incidence of gastrointestinal distress*
- *without sodium and water retention*
- *without unnatural psychic stimulation*
- *and on a lower daily dosage range*

Scored tablets of 1 mg., bottles of 50 and 500. Scored tablets of 4 mg., bottles of 30 and 100.

1. Reports to the Squibb Institute of Medical Research, 1957. 2. Sherwood, H., and Cooke, R. A.: J. Allergy 28:97, 1957. 3. Hellman, L., et al.: American Rheumatism Association. Interim session, Nov. 23, 1956. 4. Berntsen, C. A., Jr., et al.: New York Rheumatism Association. Annual meeting, April 9, 1957, New York. 5. Freyberg, R. H., et al.: International Congress on Rheumatic Diseases, June, 1957, Toronto.

SQUIBB

Squibb Quality—the Priceless Ingredient

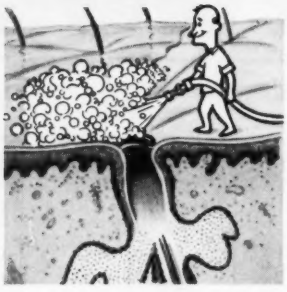
"KENACORT" IS A SQUIBB TRADEMARK

KENACORT

Squibb Triamcinolone

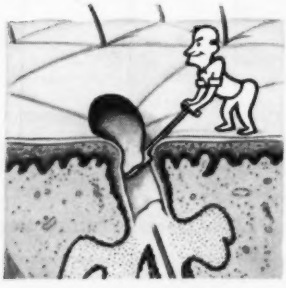
IN ACNE

Fostex® degreases the skin and helps remove blackheads

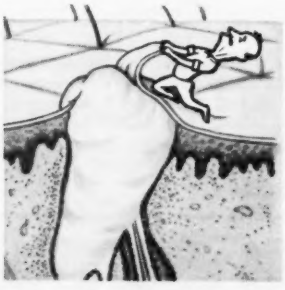


Fostex contains a combination of surface active agents (Sebulytic*) which:

◂ Completely emulsify excess oil so that it is quickly washed off the skin.



◂ Penetrate and soften comedones, unblocking the pores and facilitating removal of sebum plugs.



Fostex dries and peels the skin

◂ The Sebulytic base of Fostex dries and promotes peeling of the skin . . . actions enhanced by the keratolytic effects of micropulverized sulfur and salicylic acid.

*(Sodium lauryl sulfoacetate, sodium alkyl aryl polyether sulfonate, sodium dioctyl sulfosuccinate.)

FOSTEX CREAM
for therapeutic washing of skin in the initial phase of acne treatment, when maximum degreasing and peeling are desired.

FOSTEX CAKE
for maintenance therapy to keep skin dry and substantially free of comedones.

Fostex is easy for your patients to use

◂ Patients stop using soap on affected skin areas. Instead they use Fostex for therapeutic washing of the skin. The Fostex lather is massaged into the skin for 5 minutes—then rinse and dry.

WESTWOOD *Pharmaceuticals*
Division of Foster-Milburn Co.
468 Dewitt Street • Buffalo 13, New York

88% CURE RATE

in a wide variety of PYODERMAS

BACIMYCIN®

[BACITRACIN-NEOMYCIN]

OINTMENT

a first choice for dual antibiotic therapy

In a recent study[1] of 53 patients with various types of pyodermas, the use of BACIMYCIN Ointment "... resulted in a cure rate of 88%...." Impetigo, infectious eczematoid dermatitis, atopic eczema, secondary infections superimposed on dermatitis venenata, and folliculitis were among the common skin infections that showed marked improvement with BACIMYCIN therapy.

BACIMYCIN rarely produces sensitization or primary irritation.

Supplied in ½ oz. tubes for prescriptions; in 100 gm. jars for hospital use; in ⅛ oz. tubes for ophthalmic use. Also supplied as BACIMYCIN with Hydrocortisone, ⅛ oz. tube with applicator tip.

Literature and samples on request.

1. Greenhouse, J. M., and Ryle, W. C.: A.M.A. Arch. Dermat. & Syph. 69:366 (March) 1954.

Walker **LABORATORIES, INC.** MOUNT VERNON, NEW YORK

CULTURE MEDIA AVAILABLE

Mycosel Agar

Sabouraud's Dextrose Agar

Sabouraud's Maltose Agar

Corn Meal Agar

Potato Dextrose Agar

Sabouraud's Dextrose with Penicillin

Sabouraud's Dextrose with Streptomycin

Chlamydospore Agar

Littman's Oxgall Agar

"It is considerably cheaper to use these bottles once and discard them than to pay the labor cost of reconditioning an equal number of test tubes."

... *Practical Medical Mycology*
By J. Walter Wilson, M.D.
and Orda A. Plunkett, Ph.D.
Arch D & S 59:414, April 1949

A PREFERRED METHOD for the CULTURE of FUNGI as an OFFICE PROCEDURE

WRITE FOR INFORMATIVE LITERATURE

DERM MEDICAL Sterile Glass Containers holding Sabouraud's Dextrose Agar offer a simple, accurate method for the culture of fungi pathogenic to man. When indicated for diagnosis and study of mycotic diseases, can be used as a routine office procedure. For institutional use, this method has proved both efficient and economical.

Derm Medical

Manufacturers of Culture Media in Sterile Containers

DM 3-4

DEPT. "D", P.O. BOX 78595 • WEST ADAMS STATION • LOS ANGELES 16, CALIF.